Increasing Referral for Renal Transplant Evaluation in Recipients of Nonrenal Solid-Organ Transplants: A Single-Center Experience

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The use of cyclosporine and tacrolimus therapy in nonrenal (heart, heart/lung, lung, and liver) transplantation has resulted in improved patient and graft survival. Nephrotoxicity is one of the major side effects of tacrolimus and cyclosporine therapy and may lead to ESRD. The trend of referral of nonrenal solid-organ transplant recipients for kidney transplant evaluation at a large multiorgan transplant center was examined. Records of all patients who were referred for renal transplantation at the University of Alabama between January 1, 1993, and June 30, 2004, were reviewed. Eighty (0.96%) of 8318 individuals had previously undergone a nonrenal solid-organ transplant and were included in the study. The majority (72%) of patients had their nonrenal transplants performed at the University of Alabama. Twenty-two patients had their nonrenal transplant performed elsewhere and had fewer data available for analysis. From the period 1993–1996 to 2001–2004, an 11-fold increase in the absolute number of referrals of patients with nonrenal transplants was noted. Of patients who were referred for transplant evaluation, 25 became recipients of kidney transplants with a predominance of living-donor transplants. Referral for kidney transplant evaluation among nonrenal solid-organ transplant recipients is increasing and will exacerbate the existing shortage of deceased-donor kidneys that are available for transplantation. There was a trend for liver transplant recipients compared with other solid-organ recipients to develop ESRD at a greater rate.


The introduction of calcineurin inhibitor (CNI)-based immunosuppression in the early 1980s has revolutionized the field of organ transplantation. Cyclosporine (introduced in 1984) and tacrolimus (introduced in 1995) have remained the foundation of immunosuppressive therapy in patients who receive renal and nonrenal transplants. As patient survival has increased, the enthusiasm for CNI-based immunosuppression has been tempered by chronic irreversible nephrotoxicity with progression to ESRD in some patients (1). Recent studies have suggested that 2 to 18% of patients who receive heart, lung, or liver transplants develop severe renal insufficiency, and approximately half of these patients will progress to ESRD by 10 yr after engraftment (2–4). The substantial range in the prevalence of renal insufficiency likely is attributable to a varying definition of chronic kidney disease (CKD) in the literature and may reflect variability in immunosuppressive dosing and drug levels.

As renal failure is increasingly recognized as a complication of nonrenal solid-organ transplantation, referral for potential kidney transplantation has become common. Recent studies have demonstrated that, as in the dialysis population, kidney transplantation confers a significant survival advantage in patients with ESRD (5,6). In this study, we sought to examine the rates of referral for ESRD among recipients of various nonrenal solid organs, the causes of renal failure among those who were referred for evaluation, and the fates of these patients including potential kidney transplantation. Because occurrence of CKD is a relatively poor end point (all patients who are on CNI have some degree of renal insufficiency), a more defined end point was used: Referral to a kidney transplant evaluation service for possible kidney transplantation.

Materials and Methods

Patients

In 2002, after approval from the Institutional Review Board, records of all adult (older than 18 yr) patients who had been referred for kidney transplant evaluation at the University of Alabama at Birmingham from January 1, 1993, to August 31, 2004, were reviewed. In addition, to establish the time incidence of ESRD in our institution, we reviewed records of all adult nonrenal transplants that were performed at the University of Alabama at Birmingham. Excluded from the analysis were recipients of primary heart-kidney transplants, recipients of primary liver-kidney transplants, solitary pancreas transplants, and kidney-pancreas transplants. During the duration of each respective program, 684 heart transplants, 27 heart-lung transplants, 341 lung transplants, and 1006 liver transplants were performed at our institution through June 2004 (Table 1). Patients who received a transplant
elsewhere did not have data about renal function at the time of solid-organ transplantation, and records of nephrologic evaluation were not available.

Data that were recorded upon chart review included race; type of nonrenal solid-organ transplant; measurements of renal function at the time of transplantation, including 24-h urine collection and iothalamate GFR if available; immunosuppressive therapy; comorbid conditions; date and components of nephrologic evaluation, including native-kidney biopsy; date and value of most recent creatinine level; date of kidney transplant evaluation; and subsequent kidney transplantation. After the review, data were collected prospectively for these patients as well as for new patients who were referred for transplant evaluation. Ascertainment of death was accomplished by performing a search of the Social Security Death Master File as of the end of May of 2005 using all study individuals.

**Statistical Analyses**

Statistical analysis was performed using the InStat (GraphPad Software, San Diego, CA) statistical analysis package. χ² and unpaired t test analyses were performed, as appropriate. ESRD-free survival and patient survival curves were constructed using the product-limit method (Kaplan-Meier). Differences among survival curves were estimated by the log-rank test. SPSS for Windows version 11.1 (SPSS Inc., Chicago, IL) was used in these analyses. A two-sided P < 0.05 was considered statistically significant.

**Results**

**Patient Population**

A total of 8318 patients were evaluated for renal transplantation during the study period. Eighty (0.96%) patients met inclusion criteria, 22 of whom received their nonrenal transplant outside our institution. Of these 22 patients, 16 were liver transplants, three were heart transplants, and three were lung transplants. Data on 2058 nonrenal transplant recipients were reviewed to establish the proportion of patients who were free from ESRD during the observation period. A more detailed review of the data concerning the 58 patients who received a transplant at our institution was undertaken.

Baseline demographic data of the 58 study patients are shown in Table 2. Mean ± SD age was 55.6 ± 8.6 yr (range 31 to 70 yr). The recipients included 53 white, four black, and one Asian. Thirty patients had liver transplants, 19 had heart transplants, two had heart-lung transplants, and seven had lung transplants. One patient received a heart-kidney transplant after primary heart transplantation. The mean serum creatinine at the time of the nonrenal solid-organ transplantation was 1.25 ± 0.46 mg/dl with a creatinine clearance by the Cockroft-Gault equation of 80.5 ± 36.4 ml/min. The mean time from nonrenal solid-organ transplantation to kidney transplant evaluation in all recipients was 7.3 ± 4.0 yr. At the time of kidney transplant evaluation, 27 patients were on dialysis. The 31 patients who were not on dialysis had an average estimated creatinine clearance of 21.7 ± 14.7 ml/min.

**Immunosuppression**

Immunosuppression for lung transplant patients consisted of a cyclosporine-based regimen from the inception of the program to year 2000. Afterward, daclizumab induction was used in conjunction with tacrolimus-based immunosuppression. Similar immunosuppression was used in heart-lung transplant recipients and heart transplant recipients, and rabbit anti-thymocyte globulin was used in the early heart-lung and heart transplant recipients. For these recipients, tacrolimus-based immunosuppression is initiated at 0.5 mg twice daily and titrated to target levels of 10 to 15 ng/ml at 1 mo, 5 to 10 ng/ml at 6 mo, and 5 to 10 ng/ml at 12 mo.

Immunosuppression for liver transplant recipients consisted of a cyclosporine-based regimen with azathioprine and prednisone from the inception of the program in 1989 to 1994. Tacrolimus replaced cyclosporine in 1995, and mycophenolate mofetil was used as the antimetabolite. The current protocol consists of tacrolimus monotherapy by the first year after transplantation, with discontinuation of mycophenolate mofetil and prednisone in the majority of patients. For these recipients,
tacrolimus-based immunosuppression is initiated at 2 mg orally twice daily and titrated to target levels of 8 to 10 ng/ml at 1 mo, 5 to 8 ng/ml at 6 mo, and 4 to 6 ng/ml at 12 mo.

In summary, most liver and lung transplant recipients were on a tacrolimus-based regimen, and most heart and heart-lung patients were on a cyclosporine-based regimen. Immunosuppressive trough levels were not evaluated given the significant variability in assays during the period of transplantation for the study patients. For patients who received a transplant outside our institution, immunosuppression consisted of 17 patients who were on cyclosporine therapy (13 liver, three heart, and one lung) and five patients who were on tacrolimus therapy (three liver and two lung).

Cause of Renal Failure

Sixteen (28%) of the 58 patients underwent a native-kidney biopsy before kidney transplantation, although for one, the sample that was obtained was insufficient for diagnosis. The majority of diagnoses were focal segmental glomerulosclerosis (FSGS; n = 3), CNI toxicity (n = 3), and advanced nephrosclerosis (n = 3). Other diagnoses included diabetic nephropathy (n = 1), diabetic nephropathy in combination with FSGS and CNI toxicity (n = 1), diabetic nephropathy in combination with malignant hypertension (n = 1), membranoproliferative glomerulonephritis type I (n = 1), immunotactoid glomerulopathy (n = 1), mesangial glomerulonephritis (n = 1), and inadequate tissue (n = 1). The type of transplants included heart (n = 5), heart-lung (n = 1), liver (n = 9), and lung (n = 1). None of the 22 patients who received nonrenal allografts at other institutions had a history of native-kidney biopsy.

Mean proteinuria at the time of nephrologic evaluation for the patients who had a kidney biopsy and a 24-h measurement available (10 of 16 patients) was 6127 ± 7118 mg/d (range 422 to 24,400 mg). Mean 24-h proteinuria for patients who did not have a kidney biopsy and were presumed to have CNI toxicity (29 of 42 patients) was 1595 ± 1459 mg/d (range 148 to 4982 mg). The difference in proteinuria between the patients who had a kidney biopsy and those who had was significant (P = 0.002).

Proteinuria also was evaluated among the nonrenal organ subgroups. These results are summarized in Table 3.

Referral for Kidney Transplant Evaluation

Figure 1 details the increasing referral of nonrenal organ transplant recipients to our Kidney Transplant Evaluation Service. The year 2004 includes all referrals for that year. Seven patients who were referred after June 30, 2004, were not included in the study but are shown to illustrate the yearly trend.

Four recipients of a nonrenal transplant were referred during the period between 1993 and 1996, 32 between 1997 and 2000, and 46 between the 2001 and 2004. These referrals accounted for 0.2, 1.3, and 1.2%, respectively, of all kidney transplant evaluations that were performed during the same time intervals.

The incidence of ESRD grouped by type of nonrenal solid organ is illustrated in Table 1. Review of the heart, heart-lung, and lung transplant registries suggested that all patients who had ESRD and were medically suitable for transplantation were referred for kidney transplant evaluation. Review of the liver transplant registry revealed that seven patients with ESRD were not referred for kidney transplant evaluation, with a cumulative incidence of 3.67%. All patients who developed ESRD were accounted for in this analysis, which included patients who were referred to outside transplant centers for kidney transplant evaluation. $\chi^2$ analysis and log-rank test for trend did not demonstrate a statistically significant difference in the proportion of patients in each group who developed ESRD.

Deaths among Patients on Waiting List

Nineteen patients who were evaluated for transplant evaluation died before receiving a kidney transplant. Of these, 13 had been deemed suitable for placement on the kidney transplant waiting list. The causes of mortality were cardiovascular, infection, and malignancy.

Freedom from ESRD after Heart, Heart-Lung, Lung, and Liver Transplantation

Kaplan-Meier survival curves for freedom from ESRD in heart, heart-lung, liver, and lung transplants are shown in

### Table 3. Proteinuria by biopsy status and type of extrarenal organ transplant

<table>
<thead>
<tr>
<th>Type of organ transplanted</th>
<th>Proteinuria Mean (Range); g/d</th>
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<tbody>
<tr>
<td>Kidney biopsy</td>
<td>6.1 ± 7.1 (0.4 to 24.0)</td>
</tr>
<tr>
<td>No kidney biopsy</td>
<td>1.6 ± 1.5 (0.1 to 5.0)$^a$</td>
</tr>
<tr>
<td>Heart (n = 12/19)</td>
<td>2.7 ± 1.8 (0.1 to 5.7)</td>
</tr>
<tr>
<td>heart-lung (n = 2/2)</td>
<td>1.4 ± 1.2 (0.5 to 2.2)</td>
</tr>
<tr>
<td>liver (n = 21/30)</td>
<td>3.4 ± 5.5 (0.1 to 24.0)$^b$</td>
</tr>
<tr>
<td>lung (n = 4/7)</td>
<td>0.5 (0.3 to 0.6)</td>
</tr>
</tbody>
</table>

$^aP = 0.002$, kidney biopsy versus no biopsy.
$^bP = 0.588$, heart versus liver transplant, Mann-Whitney $U$ test.
Figure 2. These data were computed from the database of all heart, heart-lung, liver, and lung transplant recipients available from the respective transplant registries at our institution. As noted, the majority of patients were free from ESRD during the observation period.

**Subsequent Kidney Transplantation**

At the end of the study period, 25 (43.1%) patients had received kidney transplants. Of these, nine were from deceased donors, five were from living-unrelated donors, and 11 were from living-related donors. A total of 64% of patients received living-donor transplants. Eight (32%) patients (three heart recipients, two liver recipients, and three lung recipients) who received kidney transplants have subsequently died.

**Discussion**

Our data provide a uniform end point for estimating the incidence of advanced chronic kidney disease (stages IV and V) among recipients of nonrenal solid-organ transplants at a single center. It is not surprising that regardless of the type of transplanted organ, similar factors affect renal function, namely preoperative and intraoperative renal function, perioperative events, and CNI exposure (3). Our data suggest that before transplantation, some patients have stages II and III CKD (7) that increases the risk for further decline in renal function as a result of CNI-associated nephrotoxicity.

Most of the patients who were referred for evaluation were presumed to have CNI-induced renal failure, but only a minority from our center and none elsewhere had undergone renal biopsy. Those with massive proteinuria were more likely to have had a kidney biopsy. Patients with lesser proteinuria and no biopsy were presumed to have had CNI toxicity as the cause of renal failure. It is interesting that the renal biopsies demonstrate a wide spectrum of renal disease.

Although presumed CNI toxicity was the main cause of renal failure in our population, glomerular diseases remain an underappreciated cause of renal dysfunction. In the subset of patients who had undergone a kidney biopsy (28%), FSGS, mesangial glomerulonephritis, membranoproliferative glomerulonephritis, and diabetic nephropathy likely would not have been entertained as the primary renal diagnosis. We suggest that a native kidney biopsy should be performed whenever possible to assist in the diagnosis of renal failure and gauge the risk for development of recurrent disease (8–10). Liver transplant recipients, in particular, seem to have a high frequency of glomerular abnormalities without significant clinical or biochemical evidence of renal dysfunction (11,12).

Because the heart and liver transplant groups tend to have patients who have been treated predominantly with cyclosporine or tacrolimus, respectively, it is of interest that freedom from ESRD was different in both groups (Figure 2). The liver transplant population has two factors that might be expected to alter the frequency. The first is that such patients are more likely to have glomerulonephritis (especially those with hepatitis C) and, in our study, to have greater proteinuria than other patients. The second is the more frequent exposure of the liver transplant patients to tacrolimus. Our data, however, although showing a slight trend for more ESRD in the liver transplant patients does not show a significant difference. We suspect that both CNI were equal in nephrotoxic effect. In our opinion, it is most likely the greater risk for glomerulonephritis that provides the slightly greater rate of ESRD for the liver patients. Our data cannot differentiate these two factors.

The diagnosis of CNI-induced renal disease in nonrenal transplant patients is mainly presumptive. Clearly, greater availability of biopsy evidence would provide more accurate data. Nonetheless, the increasing referral of such patients to an ESRD treatment program is striking. It is likely that the same process is even more pronounced among kidney transplant recipients, but even with a biopsy, it may be difficult to ascertain whether the kidney scarring is from CNI toxicity, “chronic rejection,” or recurrent disease. A recent review demonstrated the difficulties in ascertaining the extent to which CNI-mediated nephrotoxicity is likely to have glomerulonephritis (especially those with hepatitis C) and, as in our study, to have greater proteinuria than other patients. The second is the more frequent exposure of the liver transplant patients to tacrolimus. Our data, however, although showing a slight trend for more ESRD in the liver transplant patients to tacrolimus, respectively, it is of interest that freedom from ESRD was different in both groups (Figure 2). The liver transplant population has two factors that might be expected to alter the frequency. The first is that such patients are more likely to have glomerulonephritis (especially those with hepatitis C) and, as in our study, to have greater proteinuria than other patients. The second is the more frequent exposure of the liver transplant patients to tacrolimus. Our data, however, although showing a slight trend for more ESRD in the liver transplant patients does not show a significant difference. We suspect that both CNI were equal in nephrotoxic effect. In our opinion, it is most likely the greater risk for glomerulonephritis that provides the slightly greater rate of ESRD for the liver patients. Our data cannot differentiate these two factors.

Severe CKD after nonrenal solid-organ transplantation is becoming a commonly recognized clinical entity. Increasing referrals for transplant evaluation underscore this trend as time after transplantation increases (14,15). Magee et al. (16) made a strong case for efforts to clarify the potential public health effects of transplant-related kidney disease and to consider these in cost calculations of a nonrenal organ transplant. Kidney transplantation in patients with ESRD after transplantation of a nonrenal organ is becoming increasingly common. Twenty-five patients in our series had received kidney transplants with a clear predominance of living donor allografts. The superiority of kidney transplantation over maintenance dialysis has been suggested by the recent analysis of the Scientific Registry of Transplant Recipients (5).

A single-center review of this trend has the advantages over registry data in that the end point of referral to a kidney transplant evaluation program is clear. Data using impaired renal function as the marker can result in a wider range of estimates because some impairment is expected for all patients who are on CNI therapy (17). Single-center data also can pro-
vide useful insights into immunosuppressive regimens (cyclosporine versus tacrolimus), renal function pretransplantation, proteinuria measurements, and native-kidney biopsy status.

Recent studies and reviews have explored various factors that predispose patients to CKD and the potential development of ESRD. Ishani et al. (18), in a systematic review of 219 lung and heart-lung transplant recipients, demonstrated that factors that were associated with the time to doubling of serum creatinine (used as a surrogate marker for the development of ESRD) were the serum creatinine value at 1 mo after transplantation and diastolic BP readings >90 mmHg. The overall incidence of ESRD in this population was 7.3%. In addition, Gonwa et al. (19) reported an incidence of CKD of 8.6% and ESRD of 9.5% at 13 yr in 1727 liver transplants that were performed in 1563 patients. Clearly, development of ESRD after nonrenal transplantation represents a complex interplay among multiple preoperative, intraoperative, postoperative, and long-term risk factors (13).

**Conclusion**

We have observed a trend of increasing number of patients who have had nonrenal solid-organ transplants and been referred for formal (in hospital) evaluation for kidney transplantation at our center. Although the presumptive diagnosis of cause of renal failure in these patients is CNI toxicity (both cyclosporine and tacrolimus), the histologic confirmation of that diagnosis most often is not available. When biopsy material is available, it is usually from patients who also have massive proteinuria and demonstrates a spectrum of renal diseases. It seems that the complication of renal failure is becoming an increasing problem for heart, lung, and heart-lung transplant recipients and is especially pronounced among liver transplant recipients.

**Acknowledgments**

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**References**