Antihypertensive Medication and Renal Allograft Failure: A North American Pediatric Renal Transplant Cooperative Study Report

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Abstract. Hypertension after renal transplantation occurs commonly and, in adults, is associated with decreased graft survival. The North American Pediatric Renal Transplant Cooperative Study database was analyzed to determine: (1) the percent use of antihypertensive (anti-HTN) medication based on donor type, race, age, and acute rejection status; and (2) whether use of anti-HTN medication is associated with higher rates of subsequent graft failure. Data regarding anti-HTN medication use was available in 5251 renal allografts (4821 patients) with >30 d graft function. Posttransplant follow-up data were collected at 30 d, 6 mo, 12 mo, and then annually for 5 yr. At each follow-up, patients were selected for further analysis if the graft was functioning at that visit and subsequent follow-up data were available. Overall, anti-HTN medication use was 79% on day 30 and 58% at 5 yr. At each follow-up, anti-HTN medication use was higher (P < 0.01) for cadaveric donor versus living related donor, blacks versus whites, age >12 versus <12 yr, and ≥1 versus 0 acute rejection episodes. Anti-HTN medication use at each annual follow-up was associated with significantly higher rates of subsequent graft failure. Multiple regression analysis controlling for all factors associated with increased use of anti-HTN medications revealed a relative risk of graft failure for use of anti-HTN medication of greater than 1.4 (P < 0.001). In recipients of cadaveric allografts, only acute rejection status predicted subsequent graft failure more strongly than use of anti-HTN medications. These data suggest that hypertension after renal transplantation in children, as evidenced by use of anti-HTN medications, is associated with increased rates of subsequent graft failure.

The prevalence of hypertension in patients who have undergone renal transplantation has been reported to be as high as 80% (1–3). Multiple factors may contribute to this hypertension, including preexisting hypertension due to the primary renal disease, treatment with corticosteroids and cyclosporine, renal artery stenosis in the transplanted kidney, acute or chronic rejection, and decreased functional renal mass. Posttransplant hypertension is likely an important contributing factor to chronic allograft dysfunction. It has been reported that hypertension increases the rate of renal function loss in patients with chronic renal insufficiency (4). Posttransplant hypertension in adults is associated with faster rates of decline in creatinine clearance and a greater likelihood of return to dialysis or death (3,5,6). In addition, the degree of hypertension posttransplantation is negatively associated with renal allograft survival (7–9).

In children, hypertension after renal transplantation also occurs commonly (10–14). It has been reported that antihypertensive (anti-HTN) medications are required in 70% of pediatric patients at 1 mo posttransplant, and in 59% at 24 mo posttransplant (11). However, no studies in children have systematically investigated the factors that may increase the risk for posttransplant hypertension or have determined the effect of posttransplant hypertension on long-term renal allograft survival. To further examine these questions, we analyzed the North American Pediatric Renal Transplant Cooperative Study (NAPRTCS) database to determine the clinical variables that predispose to use of posttransplant anti-HTN medications and the relationship between the requirement for anti-HTN medications and long-term graft survival.

Materials and Methods

Patients

The NAPRTCS is comprised of a Clinical Coordinating Center, a Data Coordinating Center, and more than 140 centers treating children with chronic renal insufficiency, end-stage renal disease (ESRD), and renal transplants in the United States, Canada, Mexico, and Costa Rica. Participating centers voluntarily provide clinical data regarding patients in their care 1 mo after transplantation and then every 6 mo thereafter. The data analyzed for this study were current through January 1998 and summarize the clinical information on 5251 pediatric renal transplants (4821 patients) with at least 30 d of graft function for which complete information was available on the use of...
ant HTN medications. Specific information on the number, types, or doses of anti-HTN medications was not available for this analysis.

The overall frequency of use of anti-HTN medications posttransplant was determined for all transplants and separately for recipients of living donor (LD) and cadaveric donor (CAD) allografts at 30 d, 6 mo, 12 mo, and then every 12 mo for 5 yr. The relative percent use of anti-HTN medications was also determined for different subsets of patients grouped by specific clinical variables. Patients were grouped by race (white, black, Hispanic), recipient age (0 to 1 yr, 2 to 5 yr, 6 to 12 yr, >12 yr), nephrectomy status (presence or absence of native renal tissue), and acute rejection status (presence or absence of at least one rejection episode). Patients were also grouped by the year that the transplant was performed from 1987 through 1996. For each clinical variable, the percent use of anti-HTN medications was determined both for all transplants and separately for LD and CAD. The effect of cyclosporine dose (mg/kg per d) on use of anti-HTN medications was determined by comparing the mean daily dose at each postransplant follow-up time between patients who were or were not receiving anti-HTN medications.

The relationship between use of anti-HTN medications and graft survival was determined for all patients and separately for LD and CAD. For each postransplant follow-up time point, patients were selected for further analysis if their graft was functioning at that visit, and further follow-up was available. Subsequent graft survival was then determined based on the use of anti-HTN medications at that visit. Thus, the data at each successive postransplant visit represent a subset of the data from the prior visit, less patients lost to follow-up and grafts that failed in the intervening period.

**Statistical Analyses**

To take into account the intrapatient correlation in outcomes attributable to repeat transplantation or serial clinical assessments over time, generalized estimating equations (15,16) were used to test for statistical differences between patient groups for continuous and binary response variables, as described below. In time-point-specific (i.e., cross-sectional) analyses, either normal or binomial error distributions were selected, depending on the response variable, and an exchangeable correlation structure was assumed. Multiple regression analyses were performed to evaluate further the univariate results obtained in the cross-sectional analyses. A lag-1 autoregressive correlation structure was assumed for these longitudinal analyses. Cox regression analyses of time to graft failure were performed to assess the simultaneous effects of the patient and clinical variables considered in this study. The effects of anti-HTN medication use and acute rejection status were evaluated as time-dependent covariates in these models. That is, each patient’s contribution to the likelihood of graft failure as a result of anti-HTN medication use or experiencing an acute rejection episode is based on the patient’s most recent status just before graft loss or last known follow-up visit. Only the index graft, which is the first transplant reported to the registry for each patient, was used in the Cox regression analyses.

The generalized estimating equations multiple regression models included terms for time, donor source, transplant year, recipient race and age at transplantation, native nephrectomy status, acute rejection occurrence, and cyclosporine dose. The Cox regression analyses of transplant failure included the following risk factors for graft loss: recipient race and age, prior transplantation, lifetime random transfusion history, use of anti-T cell antibody preparation, HLA-B and -DR mismatches, prior dialysis, native nephrectomy status, and, for cadaveric donor models, donor age and cold storage time.

**Results**

The overall percentage of patients receiving anti-HTN medications at various time intervals posttransplant was determined for all transplants and separately for LD and CAD allografts. For all transplants, the use of anti-HTN medications decreased from 74% (3259 of 4383) at 6 mo to 58% (652 of 1124) at 5 yr for patients with functioning grafts. At every time interval post-transplant from 30 d to 5 yr, percent use of anti-HTN medications was higher for recipients of CAD grafts compared with LD grafts (P < 0.001). Five years after transplantation, the percentage of patients receiving anti-HTN medications was 65% (347 of 536) for recipients of CAD donor grafts compared with 52% (305 of 588) for LD donor grafts (P < 0.001). When comparing patients grouped on the basis of other demographic and clinical variables, the percent use of anti-HTN medications was higher for CAD compared with LD transplants for each variable analyzed. Figure 1 shows the summary of the overall percent use of anti-HTN medications at 1 yr and 5 yr post-transplant for the variables race, age at transplant, acute rejection status, and native nephrectomy. The percentage of patients receiving anti-HTN medications was also determined based on the year of transplantation. Overall, the use of anti-HTN medications posttransplant increased from 1987 to 1996. In 1987, percent use of anti-HTN medications was 74% at 1 mo, 70% at 6 mo, and 61% at 12 mo. In 1996, the percent use had increased to 86, 78, and 76%, respectively.

The percent use of anti-HTN medications grouped by race is shown in Table 1. The use of anti-HTN medications was significantly higher for black patients than for whites or Hispanics (P < 0.001). This higher percent use for black patients was found when considering all transplants or LD and CAD transplants separately (data not shown). Five years after transplantation, the percent use of anti-HTN medications was 73% (90 of 123) for black patients compared with 56% (458 of 812) for white patients (P < 0.001).

The percent use of anti-HTN medications grouped by recipient age at transplant is shown in Table 2. The use of anti-HTN medications was higher in older recipients compared with younger recipients (P < 0.001). Virtually without exception, at each time interval postransplant the percent use of anti-HTN medications showed an increase with recipient age from <1 yr progressively through the age intervals of 2 to 5 yr, 6 to 12 yr, and >12 yr. Five years after transplantation, the percent use of anti-HTN medications was 68% (192 of 281) for patients receiving grafts at >12 yr of age compared with 44% (31 of 70) for patients receiving grafts at <1 yr of age (P < 0.001).

The percent use of anti-HTN medications grouped by the presence or absence of native kidneys is shown in Table 3. For all time intervals postransplant beyond 1 mo, use of anti-HTN medications was higher among patients with intact native kidneys at the time of transplantation. This higher percent use in patients with intact native kidneys was found when considering all transplants or LD and CAD transplants separately (data not shown). Four years after transplantation, use of anti-HTN medications was 60% (690 of 1150) for recipients with intact native kidneys compared with 51% (213 of 421) for recipients...
without native kidneys ($P < 0.001$). However, the overall effect of the presence of native renal tissue on the use of anti-HTN medications was not significant.

The percent use of anti-HTN medications grouped by acute rejection status is shown in Table 4. Patients were grouped according to their acute rejection status at each time point. Data for a patient who had experienced an acute rejection episode were analyzed with the "$\geq 1$ Rejection" group at all time points subsequent to the first rejection. The use of anti-HTN medications was significantly higher in patients with at least one reported acute rejection episode ($P < 0.001$). This higher percent use in patients with acute rejection was found when considering all transplants or LD and CAD transplants separately (data not shown). Five years after transplantation, use of anti-HTN medications was 64% (446 of 701) in patients with at least one rejection episode compared with 49% (206 of 423) in patients without rejection episodes ($P < 0.001$).

The mean cyclosporine dose was compared after grouping patients based on the use of anti-HTN medications. Cyclosporine dose decreased with time from 1 mo to 5 yr posttransplant for all treated patients. No significant differences in cyclosporine dose were observed when comparing patients on the basis of use of anti-HTN medications at any time interval posttransplant when considering all transplants or LD and CAD transplants separately.

The rate of subsequent graft failure based on use of anti-HTN medications at each time interval posttransplant is shown in Table 5. From 12 mo to 5 yr posttransplant, patients who were receiving anti-HTN medications at each annual posttransplant follow-up had significantly higher rates of subsequent graft failure. This higher rate of graft failure was found when considering all transplants or LD and CAD transplants separately (data not shown). Three years after transplantation, the rate of subsequent graft failure was more than twice as high in patients receiving anti-HTN medications (17%) compared with patients who were not (8%) ($P < 0.001$). A progressive decline in subsequent graft failure from 1 mo through 36 mo was observed in patients who were not receiving anti-HTN medications, whereas subsequent graft failure remained relatively constant during this same time period in patients who were receiving anti-HTN medications.

The relative risk of graft failure was determined separately for LD and CAD grafts. The use of anti-HTN medications,
acute rejection status, and race were each found to be simultaneous significant predictors of graft failure after including multiple clinical factors in the regression model. For LD grafts, the relative risk of graft failure was 2.14 for blacks compared with whites, 1.42 for use of anti-HTN medications, and 2.63 for $\geq 1$ acute rejection (Table 6). For CAD grafts, the relative risk of graft failure was 1.25 for blacks compared with whites, 1.58 for use of anti-HTN medications, and 2.82 for $\geq 1$ acute rejection (Table 6). In recipients of CAD grafts, only acute rejection status was a stronger predictor of graft failure than use of anti-HTN medications among all clinical variables analyzed.

### Discussion

Hypertension after renal transplantation is a well recognized phenomenon that has been described in both adults (3,17–20) and children (10–14). Estimates of the prevalence of posttransplant hypertension vary due to factors that include the number and type of patients studied, how long after transplantation the study was performed, and whether the study was performed before or after the introduction of cyclosporine as routine immunosuppressive therapy (1–3). The NAPRTCS clinical database, which includes more than 5000 patients and spans over 10 yr of clinical practice, is the largest data set available for the study of pediatric renal transplantation. In our analysis of the NAPRTCS database, we examined the use of anti-HTN medications both as a indicator of the presence of hypertension and to provide a measure of trends in the use of anti-HTN medications over a 10-yr period. A previous study from NAPRTCS on a randomly selected subset of patients found a 70% prevalence of posttransplant use of anti-HTN medications at 1 mo that decreased to 59% at 2 yr (11). These percentages are similar to the results from our analysis showing a 79% prevalence of anti-HTN medications use at 1 mo and 63% at 2 yr.

The percent use of anti-HTN medications increased during the 10-yr period from 1987 to 1996. Twelve months posttransplant, use of anti-HTN medications in 1995 was 25% higher among all transplant patients and 38% higher in LD transplants compared with 1987. This 10-yr time period spans the precyclosporine and current cyclosporine eras. Several previous studies have reported that cyclosporine contributes to elevations in blood pressure after renal transplantation (21–25). It is therefore possible that the increase in the routine use of cyclosporine over time may have contributed to the greater need for anti-HTN medications. Different formulations of cyclosporine with better bioavailability and higher target cyclosporine trough levels have also become more prevalent in recent years. In addition, it is possible that the increase in variety of types and formulations of anti-HTN medications available for children over this 10-yr period has increased the use of these drugs.
Patient race had a significant effect on the use of anti-HTN medications and on graft survival. Black patients were more likely than white or Hispanic patients to have received anti-HTN medications at each follow-up time interval from 1 mo to 5 yr posttransplant, and black patients also had a higher risk of graft failure. These results are consistent with a previous study in adults which found that black recipients of CAD transplants had worse graft outcome, higher mean arterial pressure, and a trend toward a greater prevalence of hypertension when compared to whites (21). This same study found that hypertensive black renal transplant recipients had an eightfold increase in allograft failure compared with normotensive black recipients. In aggregate, these results are consistent with the finding that hypertension and ESRD due to hypertension are more prevalent in blacks than in whites in the United States (26–30).

Recipient age at transplant was found to be an important determinant of use of anti-HTN medications. The percent use of anti-HTN medications increased with recipient age at each posttransplant time point. Older children are more likely to develop ESRD and require transplantation due to systemic and/or glomerular disorders that are associated with preexisting hypertension. In contrast, younger children are more likely to develop ESRD and require transplantation due congenital and/or structural lesions that are not usually associated with preexisting hypertension. Therefore, the higher percent use of anti-HTN medications in older children may reflect the greater prevalence in older children of glomerular diseases that predispose to posttransplant hypertension.

Acute rejection status had the greatest effect on the use of anti-HTN medications of any of the clinical variables analyzed. Patients with at least one acute rejection episode were more likely to receive anti-HTN medications at each follow-up time interval from 1 mo through 5 yr posttransplant. Five years after transplantation, patients with at least one acute rejection episode were approximately 30% more likely to be receiving anti-HTN medications than patients who were rejection-free. However, it cannot be determined from this study whether acute rejection increases the need for anti-HTN medications due to changes in intrarenal hemodynamics, increased renin release, or decreased functional renal mass. A history of acute rejection was also associated with the highest relative risk of subsequent graft failure of any of the clinical variables analyzed.

The use of anti-HTN medications was independently associated with higher rates of subsequent graft failure after controlling for other risk factors such as race and acute rejection. The relative risk of graft failure associated with use of anti-HTN medications was 1.42 for LD grafts and 1.58 for CAD grafts, indicating an approximately 40 to 50% excess risk of graft failure for patients who were receiving anti-HTN medi-

<table>
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<tr>
<th>Table 5. Rates of subsequent graft failure by use of anti-HTN medicationsa</th>
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<td>Time Posttransplant</td>
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</tr>
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a The number in parentheses is the total number of patients.

<table>
<thead>
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<th>Table 6. Relative risk of renal allograft survivala</th>
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<td>Group</td>
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<td>Living donor grafts</td>
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<td>use of anti-HTN medications</td>
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<td>race (black versus white)</td>
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<td>≥1 acute rejection episode</td>
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<tr>
<td>Cadaveric donor grafts</td>
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<tr>
<td>use of anti-HTN medications</td>
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<td>race (black versus white)</td>
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<td>≥1 acute rejection episode</td>
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a Other factors in the models include >5 lifetime transfusions, recipient age, donor age, prior transplantation, use of anti-T cell antibody preparation, HLA-B and -DR mismatches, prior dialysis, native nephrectomy status, and cold storage time. RR, relative risk; CI, confidence interval.
cations. Although previous studies have yielded conflicting results regarding the relative renal protective effects of anti-HTN medications posttransplant (1,31–35), no studies have shown or suggested that use of anti-HTN medications worsen graft survival. Hypertension contributes to loss of residual renal function in both native kidneys (36) and in renal allografts (1,6,37). Furthermore, it has been previously reported in adults that increased systolic and diastolic blood pressure posttransplant are associated with a graded increase in subsequent graft failure (9) and that posttransplant hypertension is an independent risk factor for graft failure (38). It therefore seems most probable that the need for anti-HTN medications in the current study serves as marker for posttransplant hypertension that may in many cases be marginally or poorly controlled. This hypertension is both a consequence of reduced renal function and a risk for graft failure, even after controlling for reduced renal function (38). The predicted result of this vicious cycle would be an increased rate of subsequent graft loss in patients who require anti-HTN medications.

The conclusions that can be drawn from this study about the effect of hypertension on graft loss in pediatric patients are limited for several reasons. The NAPRTCS database does not currently include the actual blood pressure of patients at the time of their posttransplant follow-up. Therefore, there are no data regarding the level of blood pressure control achieved in these patients. Furthermore, the type, dose, and number of anti-HTN medications that patients received are not available. Posttransplant hypertension is clearly multifactorial and it is unclear whether the hypertension is the cause or the result of chronic allograft dysfunction (17,39). The presence of chronic rejection, an important cause of chronic graft dysfunction and a possible risk factor for posttransplant hypertension, could not be controlled for in the calculation of the relative risk of anti-HTN medication on graft failure. Nevertheless, the results from this study using the largest data set available for pediatric renal transplantation raise important questions regarding the risk factors for posttransplant hypertension in children and the effect of this hypertension on long-term graft survival. As control of acute rejection continues to improve, we must turn our attention to those factors that may cause chronic allograft dysfunction. Ultimately, further studies need to be performed to determine whether aggressive control of blood pressure with appropriate anti-HTN medications improves long-term graft survival.

Acknowledgments

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