Long-term Outcome of Renal Transplantation Patients with Henoch-Schönlein Purpura

Joyce P. Samuel,* Cynthia S. Bell,* Donald A. Molony,† and Michael C. Braun*

Summary

Background and objectives Although Henoch-Schönlein purpura (HSP) is the most common form of renal vasculitis in childhood, progression to ESRD is rare, and there are few data on outcomes of renal transplantation in patients with HSP.

Design, setting, participants, & measurements This is a matched retrospective cohort study of renal allografts using the United Network of Organ Sharing database (1987 to 2005). Of the 189,211 primary renal allografts, there were 339 with a diagnosis of HSP. The primary end point was allograft survival.

Results Compared with the remainder of the database, the HSP population was younger (25 years versus 46 years), and had a higher proportion of women (47% versus 40%), live donors (50% versus 35%), and Caucasians (77% versus 60%). Controlling for age, gender, donor source, ethnicity, and year of transplantation, death-censored graft survival for patients with HSP was 80.0% at 5 years and 58.8% at 10 years compared with 79.0% at 5 years and 55.4% at 10 years in the non-HSP population. Among patients with reported causes of graft loss, failure from recurrent disease occurred in 13.6% of patients with HSP, compared with 6.6% in the non-HSP population. When analyzing allograft survival in recipients with HSP compared with those with IgA nephropathy, there was no difference in 10-year allograft survival (58.4% and 59.3%, respectively).

Conclusions These data indicate that although there is an increased risk of graft failure attributable to recurrent disease in patients with HSP, a diagnosis of HSP has little effect on overall renal allograft survival.

Introduction Henoch-Schönlein purpura (HSP) is the most common acute vasculitis of childhood and is characterized by purpura, arthritis, abdominal pain, gastrointestinal bleeding, and nephritis. The annual incidence in children has been estimated to be 6.7 to 13.5 cases per 100,000 (1–4). HSP is much less common in adults, with an estimated annual incidence of 13 to 15 cases/1,000,000 adults, with renal involvement occurring in 32% to 85% of patients (5–8). Renal involvement has been reported to occur in 20% to 54% of children with HSP and can range from isolated hematuria and/or proteinuria to a more severe clinical course including acute nephritis, nephrotic syndrome, or even rapidly progressive glomerulonephritis (2,3,5,9–14). For the majority of pediatric patients with HSP, renal involvement is relatively benign and self-limited (15). However, it has been estimated that up to 20% of children with HSP nephritis can develop chronic kidney disease with up to 2% progressing to ESRD and ultimately requiring renal transplantation (4,10–12,16–19). Because of the rarity of HSP as a cause of ESRD, studies examining the outcomes of renal transplantation in patients have been restricted largely to isolated case reports or small single-center case series (20–28). The limited data regarding the effect of HSP on renal allograft survival have resulted in a level of uncertainty as to whether these patients should be transplanted, whether donor type affects the likelihood of recurrence, and whether HSP recurrence negatively affects graft outcome. To address these issues, we analyzed the United Network for Organ Sharing (UNOS) database to examine the effect of HSP on the survival of renal allografts compared with other allograft recipients. We also compared allograft survival in patients with HSP versus IgA nephropathy (IgAN); diseases that share many common pathologic features and in which an aberrancy in the glycosylation of IgA1 O-linked glycans have been reported (29).

Materials and Methods All of the renal transplants performed in patients with HSP for the period 1987 to 2005 were retrospectively identified in the UNOS database. The diagnosis of HSP was defined solely by the referring institution’s reporting of HSP as the cause of ESRD. All secondary or tertiary renal or multiorgan transplants

*Division of Pediatric Nephrology and Hypertension, The University of Texas Health Science Center-Houston, Houston, Texas and †Division of Renal Diseases and Hypertension, The University of Texas Health Science Center-Houston, Houston, Texas

Correspondence: Dr. Michael Braun, Department of Pediatrics, Division of Pediatric Nephrology and Hypertension, University of Texas Health Science Center at Houston, 6431 Fannin (MSB 3.121), Houston, TX 77030. Phone: 713-500-5670; Fax: 713-500-5680; E-mail: michael.c.braun@uth.tmc.edu
were excluded from analysis. A total of 339 HSP patients with primary renal transplant were identified in the data set. The demographic data and baseline characteristics of these patients were abstracted and compared with all other primary renal transplant patients in the database.

A matched cohort study design was used to evaluate graft survival. Recipients without HSP were randomly selected from among those without HSP and matched in a 3:1 ratio to HSP recipients according to age (exact year), gender, and ethnicity, as well as donor source (living versus deceased), and year of transplantation (±3 years). A total of 333 HSP recipients were matched to 999 non-HSP recipients; six individuals were not included because matches could not be identified. The primary outcome was death-censored graft survival. The data on individual causes of graft failure were abstracted manually from the data set.

A separate subanalysis was performed comparing HSP outcomes with IgAN. Another match was performed, pairing each HSP patient with one IgAN patient, matching for age category (0 to 12 years, 13 to 22 years, or 23 years and older), gender, donor source, and year of transplant (±3 years). A total of 332 HSP recipients were matched to 332 recipients with IgAN; seven individuals with HSP were not included because sufficient IgAN matches could not be identified. This study was approved by the research review board of the University of Texas Health Science Center at Houston.

Statistical Analyses
Continuous variables were reported as median with range (minimum, maximum), and compared with the Wilcoxon rank-sum test. Categorical variables were compared using the chi-squared test or Fisher exact test when expected cell counts were low. A P value of less than 0.05 was used to determine the level of statistical significance. All of the reported probability values are two-sided.

Kaplan–Meier estimates, median survival time, and the log-rank test were used for graft survival probability estimates and comparisons between groups. Survival was defined as patient alive with a functioning graft. Death-censored data were appropriate because patient death with a functioning graft was a possible outcome, making death a competing risk for graft failure.

Results
Of the 189,211 primary renal allografts contained in the database, there were 339 individuals (0.18%) with a primary diagnosis of HSP. Although the absolute numbers of primary renal transplants have increased over time, the number of primary transplants caused by HSP has remained constant over the study period, averaging 18 ± 6 per year. Compared with the remainder of the database, those patients with HSP were younger and had a higher proportion of women, live donors, and Caucasians (Table 1).

For the survival analysis, a total of 1332 primary renal transplant patients were studied; 333 with HSP and 999 recipients with other diagnoses who were matched (1:3) for factors that are known to affect graft survival: recipient age, gender, ethnicity, donor source, and era of transplantation (30). The primary diagnoses in the control group were chronic glomerulonephritis (12.9%), diabetic nephropathy (12.3%), hypertensive nephrosclerosis (7.8%), focal segmental glomerular sclerosis (6.5%), IgAN (6.4%), polycystic kidney disease (5.7%), renal dysplasia (3.9%), and other (44.5%). The HSP and the matched non-HSP groups were not different with respect to uncontrolled baseline characteristics: pretransplantation renal replacement therapy, ischemia times, human histocompatibility leukocyte antigen mismatching, human histocompatibility leukocyte antigen-DR mismatching, haplotype matching in living donor recipients, peak Panel Reactive Antibody, donor age, donor serum creatinine, type of immunosuppression, and follow-up time (Table 2).

There was no difference in overall mortality between groups with a mortality of 5.7% in the HSP cohort and 7.2% in the matched non-HSP population (P = 0.35). Death-censored graft survival (Figure 1) for patients with HSP was 80.0% at 5 years and 58.8% at 10 years compared with 79.0% at 5 years and 55.4% at 10 years in the matched

Table 1. Demographic data of all primary allograft recipients

<table>
<thead>
<tr>
<th></th>
<th>All Non-HSP in Database</th>
<th>HSP Group</th>
<th>Matched Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 188,872; 99.8%)</td>
<td>(n = 339; 0.2%)</td>
<td>(n = 999)*</td>
</tr>
<tr>
<td>Median age (range) in years</td>
<td>46 (0 to 87)b</td>
<td>25 (1 to 76)</td>
<td>25 (1 to 76)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>112,975 (59.8)b</td>
<td>262 (77.3)</td>
<td>786 (78.7)</td>
</tr>
<tr>
<td>African American</td>
<td>43,200 (22.9)b</td>
<td>14 (4.1)</td>
<td>42 (4.2)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>21,719 (11.5)</td>
<td>36 (10.6)</td>
<td>108 (10.8)</td>
</tr>
<tr>
<td>Asian</td>
<td>7,237 (3.8)</td>
<td>15 (4.4)</td>
<td>42 (4.2)</td>
</tr>
<tr>
<td>other</td>
<td>3,741 (2.0)</td>
<td>12 (3.6)</td>
<td>21 (2.1)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>113,319 (60)c</td>
<td>181 (53.4)</td>
<td>534 (53.5)</td>
</tr>
<tr>
<td>Female</td>
<td>75,553 (40)</td>
<td>158 (46.6)</td>
<td>465 (46.5)</td>
</tr>
<tr>
<td>Donor</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deceased</td>
<td>122,327 (64.8)b</td>
<td>170 (50.1)</td>
<td>498 (49.9)</td>
</tr>
<tr>
<td>Living</td>
<td>66,545 (35.2)</td>
<td>169 (49.9)</td>
<td>501 (50.1)</td>
</tr>
</tbody>
</table>

*P > 0.05 for HSP versus all variables in matched group.

bP < 0.0001 for database versus HSP.

<sup>c</sup>P < 0.01 for database versus HSP.
non-HSP population \( (P = 0.57)\). When HSP patients were compared with the matched non-HSP group and stratified according to donor source (Figure 2), there was no difference in graft survival \( (P = 0.45 \text{ for deceased donors and } P = 0.98 \text{ for living related donors})\). Neither group showed any gender bias in regard to graft survival \( (P = 0.12 \text{ for HSP and } 0.51 \text{ for matched non-HSP group}; \text{ data not shown})\).
Among patients with a reported cause of graft loss (Table 3), graft failure from recurrent disease was significantly more frequent in patients with HSP: 13.6% compared with the 6.6% recurrent disease failure rate seen in the matched non-HSP group ($P = 0.04$). Given that the absolute numbers of allograft failures from recurrent disease in the HSP populations was low, 14 failures, it was not possible to analyze risk factors for recurrence failures in the small population with a defined cause of graft failure.

To further investigate the effect of HSP on allograft survival, additional analysis was performed on a subset of primary transplant recipients with a highly homologous form of chronic glomerulonephritis, namely IgAN. In a separate subanalysis, allograft survival in 332 HSP patients was compared with a population of 332 IgAN patients, matched for age, gender, donor source, and year of transplantation. Overall death-censored graft survival was not different between the two groups (Figure 4), with graft survival of 79.5% at 5 years and 58.4% at 10 years in the HSP population compared with 79.8% at 5 years and 59.3% at 10 years in the matched IgAN cohort ($P = 0.61$). Similar to what was seen in patients with HSP, recurrent disease was reported as the cause of graft failure in 12.1% of patients with IgAN ($P = 0.83$).

**Discussion**

These data comprising the US experience over the last three decades represent the largest single case series ever reported on HSP and renal transplantation. Given the generally favorable outcomes reported with primary HSP, it is not surprising that the number of patients undergoing renal transplantation was exceedingly small, only 339 individuals. As expected these patients were significantly younger than the UNOS population as a whole, which is consistent with prior reports that the annual incidence of HSP in adults is only one-tenth of that observed in children (1). Prior studies have reported a gender difference in primary HSP, with a 2:1 ratio of men to women; however, we did not find a significant preponderance of men in the HSP transplant population in the UNOS database (53% men) (13). The HSP patients in the UNOS database were predominately Caucasian, with significantly fewer African Americans than the database as a whole. Although previous reports on HSP and transplantation have not noted this bias, this is likely a reflection of the lack of racial and ethnic diversity found in many single center reports that were performed primarily in Asia, the Middle East, and Europe (20–24,31).

To control for differences caused by primary disease epidemiology, a matched cohort control model was used to analyze allograft survival. Using a 3:1 match, a population was selected that controlled for differences in age, gender, donor source, and year of transplantation. The distribution of primary diseases in the control population reflects those expected to be found in a young adult population and avoids overrepresentation of diseases seen in a purely adult or pediatric transplant population.

Our findings that long-term allograft survival in HSP patients is equivalent to that observed in the matched
non-HSP population are consistent with results from previous single-center case series. In 2010, Han et al. (20) reported their experience with 20 HSP patients collected over a 35-year period and compared outcomes with two separate control groups (matched 1:2 with IgAN or 1:2 with all other diagnoses) controlling for age range, gender, and donor source. They showed a graft-survival rate of 95% at 5 years and 87.7% at 10 years for the HSP group, which was not statistically different from their control populations ($P = 0.209$ for the 10 years survival rate comparison). Similarly Moroni et al. (21) reported data on 19 HSP patients requiring renal transplantation over a period of 27 years. After matching 1:2 with controls for age range, gender, and donor source, they found equivalent graft survival with 15 years of follow-up; the death-censored graft-survival rate in the HSP group was 75% at 10 years compared with 70% in the control group (21). The remaining four smaller case series reported 5-year allograft survival ranging from 70% to 89% (22–26).

Previously reported rates of graft loss caused by HSP recurrence have ranged from 0% to 21% (21,23,24,32,33). In their comprehensive review of recurrent glomerulonephritis in renal transplantation, Briganti et al. (34) reported an overall incidence of graft loss caused by recurrent disease of 8.4% at 10 years. Although the allograft failure rate from recurrent HSP was estimated at 16.7%, detailed analysis was limited because only 24 recipients with HSP were contained in the ANZDATA database (34). In our study, we found that among those patients with a reported cause of graft failure, disease recurrence accounted for 13.6% of failures in the HSP population. Previously, studies have reported histologic recurrence rates of 15% to 53% after transplantation in HSP patients (20–24,32,33). Hasegawa et al. (24) reported a histologic recurrence rate in 9 of 12 (75%) of living related donor grafts and in 0 of 5 (0%) of deceased donor grafts, suggesting an increased tendency for HSP to recur in those with living related donors. They found that those with pathologic recurrence and urinary abnormalities (hematuria and proteinuria) had a 40% rate of graft loss, but those with pathologic recurrence alone (without urinary abnormalities) did not experience graft loss. Although the overall graft loss from recurrence was 2 of 17 (11.7%), which is comparable to our data (13.6%), the data are difficult to compare directly, because our data do not consider those with recurrent disease that did not progress to graft failure. We did find that the proportion of patients with recurrence as a cause of graft loss was equivalent when stratified by donor source.

Table 3. Reported causes of allograft failure in the matched groups

<table>
<thead>
<tr>
<th></th>
<th>HSP Group (n = 103; 100%)</th>
<th>Matched Group (n = 271; 100%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic allograft nephropathy</td>
<td>52 (50.5)</td>
<td>137 (50.5)</td>
</tr>
<tr>
<td>Hyperacute/acute rejection</td>
<td>18 (17.5)</td>
<td>51 (18.8)</td>
</tr>
<tr>
<td>Recurrent diseasea</td>
<td>14 (13.6)</td>
<td>18 (6.6)</td>
</tr>
<tr>
<td>Other</td>
<td>6 (5.8)</td>
<td>10 (3.7)</td>
</tr>
<tr>
<td>Noncompliance</td>
<td>4 (3.9)</td>
<td>12 (4.4)</td>
</tr>
<tr>
<td>Infection</td>
<td>4 (3.9)</td>
<td>8 (3.0)</td>
</tr>
<tr>
<td>Primary nonfunction</td>
<td>2 (1.9)</td>
<td>13 (4.8)</td>
</tr>
<tr>
<td>Graft thrombosis</td>
<td>2 (1.9)</td>
<td>14 (5.2)</td>
</tr>
<tr>
<td>Surgical/urological complication</td>
<td>1 (1.0)</td>
<td>8 (3.0)</td>
</tr>
</tbody>
</table>

aFisher exact test comparing failure caused by recurrence versus any other cause ($P = 0.04$).
The overall mortality rate was not different between the HSP group and the matched non-HSP group (5.7% versus 7.2%, P > 0.05). Cause of death information was not available in the UNOS data set. These mortality rates are lower than previously reported in the UNOS database and likely reflect a younger study population that lacks many of the co-morbidities that contribute to increased mortality in the older transplant patient population (35).

The data on recurrence failures must be viewed with caution because the criteria for failure from recurrent disease are not explicitly defined in the UNOS database. Biopsy reports are not required, and there is no information as to whether extrarenal manifestations of HSP were present or not. Pathologically, it is not possible to distinguish HSP from IgAN, and it is interesting that the rates of reported allograft failures from recurrent HSP and recurrent IgAN are almost identical. The actual rate of pathological recurrence in the UNOS population is likely much higher than 13.6%, but it is not possible to extract these data, because UNOS does not report disease recurrence except in the context of graft failure. Furthermore, when comparing graft failure attributable to recurrence from HSP, misclassification or observer bias may influence the recurrence rates that we have reported in this analysis.

Large multicenter data sets such as the UNOS database are essential when studying rare diseases but have inherent limitations as well. Certain clinical data are simply not available for analysis within the UNOS data set, including the patient’s pretransplant clinical course and biopsy reports. Furthermore, there is a lack of data on HSP extrarenal recurrence or therapeutic interventions. Thus, it is not possible to quantify overall recurrence rates, time from disease recurrence to graft loss, or risk factors for disease recurrence.

In summary, on the basis of the analysis of the UNOS database, HSP does not negatively affect graft survival. Although there is an increased risk of failure from disease recurrence, it does not appear to accelerate time to graft loss. It is likely therefore that the decline in renal function associated with recurrent HSP parallels the gradual loss of function seen in primary HSP, and thus for most patients the other causes of allograft failure are the dominant competing mechanisms of graft loss.

Acknowledgments

This work was supported in part by Health Resources and Services Administration Contract 234-2005-370011C. The content is the responsibility of the authors alone and does not necessarily reflect the views or policies of the Department of Health and Human Services, nor does mention of trade names, commercial products, or organizations imply endorsement by the US Government.

Disclosures

None.

References


Received: February 10, 2011 Accepted: April 23, 2011

Published online ahead of print. Publication date available at www.cjasn.org.