Regional Sharing for Adult Status 1 Candidates: Reduction in Waitlist Mortality

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The intent of regional sharing for status 1 candidates is to promote timely access to donor livers. Presumably this decreases waitlist mortality. Little published data exists that supports this policy. Organ Procurement and Transplantation Network data was used to calculate region 4 and national adult waitlist death and transplant rates 4 yr prior to (period A) and after (period B) implementation of the sharing agreement in July 1999. Death and transplant rates were calculated using a competing risk analysis. Regional sharing resulted in a reduction in adult status 1 waitlist death rate and an increase in transplant rate for region 4 candidates at 7 and 14 days (P < 0.05) without a change in the death rate at 90 days for the non-status 1 candidates. National data showed a significant increase in transplant rate at 7 days and reduction in waitlist death rate at 14 days after listing (P < 0.05). Status 1 waiting time was decreased from 10 to 3 days (P < 0.05). Adult patient survival was not significantly different between the periods. In conclusion, regional sharing for status 1 candidates results in an increased transplant rate and a reduction in waitlist mortality. Sharing did not impact waitlist mortality for non-status 1 candidates. Liver Transpl 12:470-474, 2006. © 2006 AASLD.

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Regional sharing for the highest priority, status 1, candidates for liver transplantation now exists in all 11 regions of the United Network for Organ Sharing. These sharing mechanisms were implemented as a consequence of the Institute of Medicine report and issuance of the Final Rule by the Department of Health and Human Services in 1999.1 The basic tenets are that the sickest patients should have the greatest access to transplantation and that waiting time should be deemphasized.2 This critically ill group of patients is defined as status 1 and strict criteria are used for its definition. These criteria include fulminant hepatic failure, hepatic artery thrombosis within 7 days of transplant, primary nonfunction of a previous hepatic allograft, or acute decompensated Wilson’s disease. The definition for pediatric patients is more liberal allowing for chronic liver disease entities to qualify if the patient is in the intensive care unit and meets specified criteria. It was recognized that these groups of patients had very high mortality without transplantation and did well if transplanted in a timely manner.3 All United Network for Organ Sharing regions were strongly encouraged to develop regional sharing agreements that might allow these status 1 candidates access to cadaveric donor livers throughout a region and not just in the local sharing unit to which the transplant center may be located.

The goal of broader sharing is to increase access for status 1 candidates to cadaveric organs in order to decrease waitlist mortality. However, little published results exist to validate the current policy. Humar et al.4 recently reported results for status 1 sharing from a single center. They showed a reduction in waitlist mortality and time to transplant. There are no other reports evaluating this policy of broader sharing for these critically ill patients and there are no other reports to determine if the single center results are unique or more uniform around the country. Since organ allocation policy development is now driven largely by data analysis and evidence-based medicine, it is imperative that
policies be evaluated after implementation to ensure that their intent is met and to facilitate refinements when deemed necessary. We herein evaluate our regional experience and the national results for broader sharing for status 1 candidates and the impact of this policy on non-status 1 patients.

METHODS

Data

Organ Procurement and Transplantation Network data was used for this analysis. We elected to concentrate on adult liver transplant candidates listed as status 1. With the small number of events in the pediatric population and the heterogeneous definition of status 1 in that patient group, a comprehensive analysis and report should be performed separately. The definition of status 1 was clarified in 1997 (Table 1). In 1999, Regional Review Boards were established to determine appropriateness of status 1 applications. This process led to the application of regional sharing for candidates who meet these criteria. Region 4, comprised of Texas and Oklahoma, initiated a regional sharing agreement on July 13, 1999. This agreement has a payback clause stipulating that once a donor service area accrues a debt of more than 3 livers imported for status 1 transplants, the next cadaveric liver allograft from that donor service area is offered to the donor service area in the region with the most credits. To assess whether regional sharing has impacted access to transplant for status 1 patients, we elected to compare a 4 yr interval prior to and after implementation of the sharing agreement. These time periods were July 13, 1995-July 12, 1999 (Period A), and November 13, 1999-November 12, 2003 (Period B). We allowed 3 months in between the 2 periods to allow for patients that were listed in the prior time period to be removed from the waiting list.

Analysis

Transplant and mortality rates for patients listed as status 1 were analyzed using a competing risk analysis. With this approach, a time point is evaluated and candidates are categorized as follows: still waiting for transplant, transplanted, death or too sick to transplant, and other. Numerous time points can be chosen and we evaluated 7, 14, 30, and 90 days after listing.

<table>
<thead>
<tr>
<th>TABLE 1. Adult Life Expectany Without a Liver Transplant of Less Than 7 Days</th>
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<tbody>
<tr>
<td>Fulminant hepatic failure defined as the onset of hepatic encephalopathy within 8 weeks of the first symptoms of liver disease. The absence of preexisting liver disease is critical to the diagnosis.</td>
</tr>
<tr>
<td>Hepatic artery thrombosis in a transplanted liver within 7 days of implantation.</td>
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The difference between categories is considered significant if the 95% confidence intervals (CIs) do not overlap. Median waiting time is calculated in days and nonoverlapping 95% CIs signify statistical significance.

RESULTS

Characteristics of Listings, Transplants, and Donor Source

In region 4 a total of 96 adults were listed as status 1 in period A and 106 adults were listed as status 1 in period B. Adult status 1 listings as a percent of total decreased from 4.6 to 3.4% ($P = 0.03$) between period A and B. Status 1 transplants comprised 6.3 and 4.3% ($P = 0.02$) of adult transplants for periods A and B (Table 2).

In study period B, after the institution of a regional sharing agreement, 56% of status 1 recipients were transplanted with a liver from a regional share compared to 23% prior to the agreement ($P = 0.001$) in Region 4. For non-status 1 recipients, the number of livers from regional sources decreased from 15 to 10% for the same time periods ($P < 0.001$). Partial allografts were used infrequently in adult status 1 recipients, yet much more commonly in pediatric recipients.

Transplant and Death Rates

Regional sharing in Region 4 resulted in an increased rate of transplant and a decreased rate of death for adult status 1 recipients at 7 days as determined by a competing risk analysis (Fig. 1A). These results were similar for the 14 day endpoint as well (Fig. 1B). The probability of death at 7 days decreased from 21.2% (95% CI, 13.3-29.1%) in period A to 13.5% (95% CI, 6.4-20.6%) for adult status 1 patients in period B. This difference was not statistically different at 7 days, 14 days or other time points tested (as determined by overlap of confidence intervals). However, when the same analysis is performed with national data, the probability of transplant at 7 days with regional sharing in time period B was 50.4% (95% CI, 48.4-52.5%) which is significantly better than the 46.5% (95% CI, 44.5-48.4%) seen prior to broader sharing in
time period A (Fig. 1C). Likewise, the probability of death at 14 days for adults decreased significantly from 21.3% (95% CI, 19.7-22.9%) in period A to 17.8% (95% CI, 16.2-19.5%) in period B with the implementation of regional sharing (Fig. 1D).

The impact of regional sharing for status 1 candidates in our region did not change the probability of transplant or death in non-status 1 candidates (Fig. 2). At the 90-day time point, the chance of transplant had decreased insignificantly from 19.0% (95% CI, 17.3-20.8%) to 18.0% (95% CI, 16.6-19.4%) and the probability of death or too sick for transplant decreased from 7.14% (95% CI, 6.00-8.28%) to 6.55% (95% CI, 5.67-7.43%) with regional sharing.

Waiting Time and Survival

There was a significant decrease in median waiting time to transplant in Region 4 from 10 days to 3 days for adult patients with regional sharing (Table 3). Waiting time was significantly longer for non-status 1 patients for the same period. Though the waiting time was longer for this group, the probability of wait list mortality did not substantially increase as already shown in Figure 2. This finding has been previously observed, namely that waiting time is not directly related to wait list mortality.

Region 4 adult status 1 six month recipient survival did not significantly change between period A and B (Table 4). Survival for the non-status 1 recipients was comparable for the 2 periods (90.7% and 92.3%). Nationally, survival for adult status 1 recipients was not significantly different (76.3% and 77.8%) and comparable to our regional survival for period B (75.7%).
DISCUSSION

The status 1 candidate is one of the most critically ill recipient for liver transplantation. By definition, these patients have a limited life expectancy of 7 days or less without transplantation. Therefore an expeditious pre-transplant period is vital to reduce mortality for this subset of candidates. The ability to access a broader pool of donor livers should give these recipients an increased chance at receiving a transplant. The redefinition of status 1 in 1997 in concordance with the establishment of Regional Review Boards brought significant changes to the process by which patients were listed as status 1. With this system in place and functional, regional sharing was then instituted for status 1 candidates. Establishment of a peer review process and tighter definition of status 1 candidates were critical elements of a system allowing patients broader access to cadaveric donor livers. With this broader access one might surmise candidates should experience an increased probability of transplant and decreased mortality on the waiting list as well as a decrease in waiting time to transplant.

No previous reports have evaluated the efficacy of the status 1 regional sharing agreements present in every United Network for Organ Sharing region. Humar el al.4 showed a beneficial impact of regional sharing on waiting times for status 1 candidates at a single center. With an in-depth analysis of our regional experience with broader sharing we have been able to demonstrate a substantial increase in the probability of transplant for adult status 1 candidates and a substantial decrease in waiting list mortality for this subset of critically ill patients. Although we did not observe statistically significant changes likely due to relatively few death events in Region 4 status 1 patients, we did find statistically significant decreases in transplant probability 7 days after listing and a statistically significant decrease in waiting list mortality in this same candidate group 14 days after listing for the national data. The waiting time for adults to transplant in our region was significantly shorter as well. In addition, we found that regional sharing for status 1 candidates did not appear to negatively impact waiting list mortality for non-status 1 candidates. This is an important point as any redistribution of a limited resource should be evaluated in its effect on the whole at risk population to truly appreciate the global impact. These data would appear to support the current policy of broader sharing for adult patients meeting the status 1 definition.

The definition of status 1 for adult candidates is quite narrow which is reflected in the limited number of patients listed and transplanted in this category. These numbers changed significantly with a decrease between period A and B in percentage of status 1 listings and transplants. This may partially be reflective of the refinement of the status 1 definition in 1997. The definition of a pediatric status 1 candidate is similar to the adult definition but also permits patients with chronic liver disease. This difference from the adult definition may account for the approximately 40% of pediatric recipients being transplanted in the status 1 category.6 Given this disparity from the adult population we felt that including the pediatric candidates might confound the results. This candidate group should be studied independently.

Waiting time to transplant in region 4 was substantially reduced with regional sharing for the adult status 1 recipient in this analysis. Wait time is not of value for non-status 1 patients,2 yet given the critical nature of many status 1 candidates (expected death in 7 days without transplant) wait time would intuitively seem to be important. Waiting time for the non-status 1 recipients was longer in Period B which likely represents the significant growth in the overall liver transplant waiting list seen in our region.

Broader sharing of cadaveric hepatic allografts for the most critically ill is practiced in all United Network for Organ Sharing regions. Some regions vary in the exact implementation of the policy yet all regions allocate livers to status 1 patients first.7 A payback mechanism is present in some regions, including ours, that may prevent one program or donor service area from incurring a significant debt due to an influx of organs from the remainder of the region. For period B in this study there were a total 79 regional shares and a total of 8 payback livers were exchanged. An argument can be made that a payback system, in the face of strict candidate criteria, is not necessary. Development of strict criteria that allow patients to access a broader source of organs is imperative to prevent abuse of the system. These steps were vital for broad based support for regional sharing for status 1 candidates. Such criteria may be necessary for any future

### Table 4. Patient Survival (6 Months)

<table>
<thead>
<tr>
<th>Region 4</th>
<th>Period 1</th>
<th>Period 2</th>
<th>( P )</th>
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<tbody>
<tr>
<td>Adult-status 1</td>
<td>81.4 (72.1, 90.8)</td>
<td>75.7 (63.7, 87.7)</td>
<td>NS</td>
</tr>
<tr>
<td>Adult-non-status 1</td>
<td>90.7 (89.0, 92.5)</td>
<td>92.3 (90.9, 93.8)</td>
<td>NS</td>
</tr>
<tr>
<td>National</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adult-status 1</td>
<td>76.3 (74.5, 78.2)</td>
<td>77.8 (75.5, 80.1)</td>
<td>NS</td>
</tr>
<tr>
<td>Adult-non-status 1</td>
<td>89.3 (88.8, 89.8)</td>
<td>90.1 (89.6, 90.6)</td>
<td>NS</td>
</tr>
</tbody>
</table>

NOTE: Survival is expressed as a percentage with 95% confidence limits.
Abbreviation: NS, not significant.
discussions regarding regional sharing for higher Model for End-Stage Liver Disease score patients.

Adult status 1 recipient survival in region 4 was not changed with the implementation of regional sharing. There was an insignificant decrease in adult status 1 recipient survival with broader sharing. Region 4 adult status 1 recipient survival in period B is comparable to adult survival for period A and B for the nation as a whole. One would not necessarily see better outcomes with broader sharing as the recipients are still critically ill with higher risks at the time of transplant. The effect of broader sharing should be more on waitlist mortality than on recipient survival as we have seen.

Our data indicates an improvement in access to cadaveric hepatic allografts for adult status 1 candidates as shown by an increase in transplant rate and reduction in waitlist mortality. Without statistical significance with our regional results, one can not say that the policy is fully substantiated in Region 4. However, the trends would suggest that this policy has had a favorable effect on waiting status 1 candidates in Region 4. The national data, where statistically significant improvements in waitlist mortality and transplantation rates were seen, support this conclusion.

Several confounding variables should be considered when analyzing these results. The time periods reported here are relatively long (4 yr each) and many advances in patient care have occurred. One can not assume that candidates and recipients in 1995 are entirely comparable to those in 2003. Changes in practice patterns and local competition may have effects that are not readily apparent. The definition of status has changed as well. Therefore, a number of different variables, difficult to control for, may or may not have had an impact on these results.

In conclusion, regional sharing for status 1 candidates has decreased the waitlist mortality for this candidate group; the intended consequence of the policy. Further refinement of the definitions of status 1 will be important to maintain the integrity and intent of the system. The structure and success of this policy might be useful in defining future sharing mechanisms to decrease waitlist mortality for non-status 1 candidates.

REFERENCES