Evidence-Based Incorporation of Serum Sodium Concentration Into MELD

SCOTT W. BIGGINS, W. RAY KIM, NORAH A. TERRAULT, SAMMY SAAB, VIJAY BALAN, THOMAS SCHIANO, JOANNE BENSON, TERRY THERNEAU, WALTER KREMERS, RUSSELL WIESNER, PATRICK KAMATH, and GORAN KLINTMALM

University of California San Francisco, San Francisco, California; University of California Los Angeles, Los Angeles, California; Mount Sinai Medical Center, New York, New York; Mayo Clinic Scottsdale, Scottsdale, Arizona; Baylor Institute of Transplantation Sciences, Dallas, Texas; Mayo Clinic Rochester, Rochester, Minnesota

See CME Quiz on page 1902.

Background & Aims: Serum sodium (Na) concentrations have been suggested as a useful predictor of mortality in patients with end-stage liver disease awaiting liver transplantation. Methods: We evaluated methods to incorporate Na into model for end-stage liver disease (MELD), using a prospective, multicenter database specifically created for validation and refinement of MELD. Adult, primary liver transplant candidates with end-stage liver disease were enrolled. Results: Complete data were available in 753 patients, in whom the median MELD score was 10.8 and sodium was 137 mEq/L. Low Na (<130 mEq/L) was present in 8% of patients, of whom 90% had ascites. During the study period, 67 patients (9%) died, 243 (32%) underwent transplantation, 73 (10%) were withdrawn, and 370 were still waiting. MELD score and Na, at listing, were significant (both, P < .01) predictors of death within 6 months. After adjustment for MELD score and center, there was a linear increase in the risk of death as Na decreased between 135 and 120 mEq/L. A new score to incorporate Na into MELD was developed: “MELD-Na” = MELD + 1.59 (135 – Na) with maximum and minimum Na of 135 and 120 mEq/L, respectively. In this cohort, “MELD-Na” scores of 20, 30, and 40 were associated with 6%, 16%, and 37% of risk of death within 6 months of listing, respectively. If this new score were used to allocate grafts, it would affect 27% of the transplant recipients. Conclusions: We demonstrate an evidence-based method to incorporate Na into MELD, which provides more accurate survival prediction than MELD alone.

Allocation of donor livers in the United States is based on a “sickest first” policy using the model for end-stage liver disease (MELD) score to define medical urgency for transplantation. The MELD, originally developed to predict mortality after transjugular intrahepatic portosystemic shunt, is based on 3 common, objective, reproducible laboratory tests, including serum total bilirubin, the international normalized ratio (INR), and serum creatinine. A number of independent studies have shown that the MELD score correlates well with short-term mortality risk in patients with cirrhosis. Since February 2002, the MELD has been used as the standard by which to determine priorities in allocating cadaveric livers to transplant candidates.

In pursuit of an evidenced-based improvement of the MELD and MELD-based liver allocation, recent single center retrospective studies have found that, in addition to the MELD parameters, serum sodium (Na) is an important additional predictor of waiting list mortality. Hyponatremia has been well described in associations with hepatorenal syndrome, ascites, and liver-related mortality. Like the components of the MELD score, serum Na is a readily available, reproducible, and objective laboratory test that predicts liver-related mortality and is therefore a reasonable candidate for inclusion in a liver allocation model.

In this study, we evaluated methods in which serum Na could be incorporated into the MELD, using a prospective, multicenter database of waiting list patients from 6 transplant programs. We present a new model, “MELD-Na,” for prediction of waiting list mortality and demonstrate the potential impact of switching from the MELD to the “MELD-Na” on allocation of available liver grafts.

Abbreviations used in this paper: INR, international normalized ratio; MELD, model for end-stage liver disease.
© 2006 by the American Gastroenterological Association Institute
0016-5085/06/$32.00
doi:10.1053/j.gastro.2006.02.010
OLT, orthotopic liver transplantation.

each local institutional review committee. Rhotic etiologies were excluded. The study was approved by liver transplantation, hepatocellular carcinoma, and noncirrhotic etiologies were included. Patients listed for fulminant hepatic failure, repeat implementation of the MELD in February 2002 are included. Patients listed for liver transplantation since 2001. In this analysis, however, only adult patients (>18 years of age) who were listed for liver transplantation since implementation of the MELD in February 2002 are included. Patients listed for fulminant hepatic failure, repeat liver transplantation, hepatocellular carcinoma, and noncirrhotic etiologies were excluded. The study was approved by each local institutional review committee.

### Materials and Methods

#### Study Subjects

This study is based on a multicenter database specifically designed for the prospective evaluation and optimization of the MELD score in predicting liver transplant waiting list mortality. Centers represented in the database include Baylor University Medical Center (Dallas, TX), Mayo Clinic (Rochester, MN, and Scottsdale, AZ), University of California Los Angeles (Los Angeles, CA), University of California San Francisco (San Francisco, CA), and Mount Sinai Medical Center (New York, NY). The database started enrolling patients in 2001. In this analysis, however, only adult patients (>18 years of age) who were listed for liver transplantation since implementation of the MELD in February 2002 are included. Patients listed for fulminant hepatic failure, repeat liver transplantation, hepatocellular carcinoma, and noncirrhotic etiologies were excluded. The study was approved by each local institutional review committee.

### Data Elements

Patient demographics, etiology of liver disease, portal hypertensive complications, and laboratory data at the time of listing were available for analysis. Listing laboratory tests were those nearest the date of listing but not more than 30 days from the date of listing. Patients were followed up until death, liver transplantation, or the last available follow-up. The MELD score was calculated according to Kamath et al, independent of hemodialysis status and without upper or lower limits in input variables or an upper limit of MELD score at 40.

\[
\text{MELD} = 11.2 \ln(\text{INR}) + 3.78 \ln(\text{Bilirubin}) + 9.57 \ln(\text{Creatinine}) + 6.43.
\]

### Statistical Methods

ANOVA and \( \chi^2 \) tests were used to compare the baseline characteristics of the study cohort between centers with level of significance of \( P < .05 \). The Kaplan–Meier method was used to estimate the overall survival rates. The log-rank test was used to compare death rates between groups.

The multivariable proportional hazards analysis was the main tool to estimate hazard ratios associated with variables in predicting the waiting list. Prognostic models were generated using mortality within 6 months of listing as the primary endpoint (ie, follow-up time was limited to 6 months). To examine the relationship between serum Na and death within 6 months, we fit a Cox regression model for survival predicted by Na, applying a P-spline smoother to the Na term, and adjusting for MELD and center. Because our aim was to describe waiting list mortality, patients were counted as a death while waiting for transplant if they (1) died while active on the transplant list, (2) were removed from the waiting list for being too sick for transplant, or (3) died within 3 months of removal from the waiting list. Others who were withdrawn or underwent transplantation were censored. Transplant center was included in all models as a stratiﬁcation variable.

### Results

#### Patient Characteristics

There were 1348 patients in the database who were screened for inclusion in the study cohort. Of these, 415 patients in the database were excluded from the analysis: 40 for fulminant hepatic failure, 99 for previous liver transplantation, 264 for hepatocellular carcinoma, and 12 for noncirrhotic etiologies. There were 933 patients who were listed for liver transplantation since implementation of the MELD on February 27, 2002, and who met the inclusion criteria. Of those, 755 patients had complete laboratory data available for this analysis and composed the study cohort. Patients with laboratory data available did not differ from those without laboratory data in their length of follow-up or death rates (\( P = .10 \) and \( P = .68 \), respectively).

The study cohort was 61% male with a median (range) age of 52 (19–73) years. Racial composition was as
follows: 82% were white, 4% Asian, 5% African American, and 9% other races (Table 1). The etiology of cirrhosis was hepatitis C in 46%, alcoholic liver disease in 15%, hepatitis B in 7%, primary sclerosing cholangitis in 5%, primary biliary cirrhosis in 4%, autoimmune hepatitis in 3%, and other etiologies in 20%. At listing, the median (range) MELD score was 10.8 (9.1–11.0) and serum Na 137 (113–148) mEq/L. The patients in the cohort had the following complications prior to the time of listing for liver transplantation: any ascites in 63%, encephalopathy in 55%, variceal bleeding in 26%, and spontaneous bacterial peritonitis in 6%.

The final cohort included 121 patients who had been included in a previous report.6 This represented 16% of the cohort. The analyses that are described in the following sections were performed with those patients included. However, separate analyses were conducted excluding the 121 patients, which did not materially alter the results (data not shown).

**Overall Survival**

At the end of follow-up, 67 patients (8.9%) died, 243 (32.3%) underwent transplantation, 73 (9.7%) were withdrawn, and 370 were still on the waiting list. The median (range) duration of follow-up was 302 (1–984) days. For the purpose of this analysis, there were 29 patients who died and 121 patients who underwent transplantation within 6 months of listing.

There were differences between the centers in race distribution but not in age or sex (Table 1). The proportion of patients undergoing liver transplantation varied by center, but the proportion withdrawn from the waiting list or who died while waiting were similar. Figure 1 compares survival experience by center. To account for measured and unmeasured differences by center, all models reported in this analysis were adjusted for center.

**Serum Na, MELD, and Waiting List Survival**

The mean and median serum Na concentrations for the entire cohort were 136.5 and 137 (standard deviation, 4.9) mEq/L, respectively. The mean and median MELD scores were 12.1 and 10.8 (standard deviation 6.6), respectively. There was modest negative correlation between serum Na and MELD score (Pearson r = −0.28, P < .01). A large majority (90%) of patients with hyponatremia (Na <130 mEq/L) had a history of ascites. On the other hand, only 11% of those with ascites also had serum Na <130 mEq/L (Figure 2).

Figure 3 illustrates the association between the risk of death within 6 months of listing and serum Na, after adjusting for MELD score and center. Decreasing serum Na was associated with increasing waiting list mortality,
independent of the MELD score. The rise in the risk of death was close to being linear between 120 and 135 mEq/L. Outside these lower and upper bounds, the effect of serum Na became smaller. The coefficient for serum Na between 120 and 135 mEq/L was $0.159 (95\% \text{ confidence interval } [CI]: 0.231 \text{ to } 0.085)$. This corresponds to a 17% increase (95% CI: 8%–26%) in the risk of death for each unit (mEq/L) decrease in serum sodium, over and above the risk corresponding to the MELD score. In contrast, the presence of ascites was not statistically significantly associated with risk of death after adjusting for the MELD score (hazard ratio, 1.6; 95% CI: 0.66 –3.8; $P = .29$).

**MELD-Na: Model Development**

There were a number of ways to incorporate serum Na data into the MELD. First, serum Na data could be made a categoric variable, eg, normonatremia vs hyponatremia (hyponatremia could also further be graded by severity). Alternatively, serum Na could be considered as a continuous variable. Second, variables that constitute the MELD score may be reexamined and their coefficients reassigned. Alternatively, the MELD score itself could be kept intact, using original coefficients for the MELD parameters.

With regard to serum Na, we compared several models in which serum Na was considered in different ways. First, as expected, using serum Na as a continuous variable yielded overall better models than when serum Na was dichotomized into normonatremia and hyponatremia. Second, among models in which serum Na was considered as a continuous variable, the optimal model may be based on a linear relationship between serum Na and risk of death within a range of serum Na concentrations. We considered several upper and lower limits for serum Na beyond which the relationship was no longer linear. The differences among the models were relatively minor, and the selection of the most useful model was based on clinical, as well as statistical significance. We chose to set upper and lower limits in serum Na at 120 and 135 mEq/L, respectively, and assumed a linear relationship between serum Na and risk of death for serum Na values between those limits. With regard to the upper limit, the cutoff value of 135 mEq/L was chosen because it appeared that the effect of serum Na gradually decreased beyond the Na level above 135 mEq/L, and it is our clinical intuition that prognosis of patients with serum Na of 135 and 140 mEq/L or higher does not differ meaningfully. The lower limit of serum Na was selected at 120 mEq/L for 2 reasons: (1) In Figure 3, one can be reasonably confident of the near linear relationship in the midportion of the graph, whereas the fit for very low values of Na was questionable primarily because of the small number of patients in our data with serum Na below 120 mEq/L; and (2), given the relatively large effect of serum Na, some type of a “cap” is necessary, as is the case with creatinine in the current MELD system.

Once the serum Na variable was defined, the survival model was refit for the MELD variables. Figure 4 compares coefficients for each of the individual components of the MELD between the refit model and the original MELD score. The refit coefficients gave slightly more weight to serum bilirubin and less weight to creatinine and INR. However, the 95% CIs of the point estimates
overlapped with those of the original MELD model, indicating that the coefficients from our new model are consistent with those of the original model. Thus, our final model incorporating serum Na and MELD was created by fitting the effect of serum Na while keeping MELD unchanged (ie, forcing a coefficient of 0.1 for MELD).

The new score, “MELD-Na,” is calculated by the following formula:

\[ \text{MELD-NA} = \frac{\text{MELD}}{1000} + \frac{1.59}{135} \times (135 - \text{Na}) \]

where the minimum value for serum Na is 120 mEq/L and the maximum 135 mEq/L. The coefficient for serum Na is 10 times that shown in the previous section in keeping with the MELD score, which was the original transjugular intrahepatic portosystemic shunt (TIPS) score multiplied by 10. The interpretation of this formula is that a 1-unit decrease in serum Na between 135 and 120 mEq/L increases the score by 1.59, ie, 1-unit decrease in serum Na is equivalent to approximately 1.6-point rise in MELD score. Thus, in patients with severe hyponatremia, the “MELD-Na” score may be larger than the MELD score by more than 20 points. However, because hyponatremia affects only a minority of patients, the concordance statistic (area under the receiver-operator curve) was not significantly higher with “MELD-Na” than with MELD (0.88 vs 0.86, respectively, \( P = .69 \)).

Figure 5 illustrates the relationship between “MELD-Na” and 6-month mortality, based on the Cox model. In our patient population of adult, primary liver transplant recipients with end-stage liver disease, a “MELD-Na” score of 20 was associated with a 6% (95% CI: 3%–9%) risk of death within 6 months of registration. A “MELD-Na” score of 30 was associated with a 16% (95% CI: 9%–22%) risk and a “MELD-Na” score of 40 with a 37% (95% CI: 22%–49%) risk.

**Impact of Na at Different Levels of MELD**

There have been suggestions that the impact of hyponatremia on survival is smaller in patients who have high MELD scores. Table 2 compares hazard ratios obtained from fitting a proportional hazards model using 6 categories of patients by their serum Na (<130 or ≥130 mEq/L) and MELD (<14, 14-20, ≥20) scores. As expected, compared with the lowest risk group (Na ≥130 mEq/L and MELD score <14), other groups have a

<table>
<thead>
<tr>
<th></th>
<th>MELD &lt;14</th>
<th>MELD ≥14 to &lt;21</th>
<th>MELD ≥21</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na ≥130</td>
<td>1 (reference) N = 498</td>
<td>3.6 (1.2–10.4) N = 146</td>
<td>13.9 (4.4–43.5) N = 48</td>
</tr>
<tr>
<td>Na &lt;130</td>
<td>7.1 (1.5–34.9) N = 22</td>
<td>23.8 (6.8–83.1) N = 14</td>
<td>18.9 (4.7–75.0) N = 25</td>
</tr>
</tbody>
</table>

NOTE. Compared with patients with normal serum sodium (>130) and low MELD score (<14), those with higher MELD score or low serum sodium had higher risk of death. Hazard ratios, 95% confidence intervals, and number of subjects in strata shown in each cell.
substantially higher risk of death. In a given MELD category, low serum Na was associated with higher risk of death. However, confidence intervals of hazard ratios for the 3 low serum Na groups were wide and overlapping with each other because of the limited number of patients. Thus, a firm conclusion may not be drawn from these data as to whether the effect of serum Na is smaller in patients with high MELD scores and, if so, at what MELD score and serum Na level that occurs.

Potential Impact of Using the MELD-Na for Graft Allocation

Figure 6 shows the relation between the “MELD-Na” and the MELD. Bisecting lines represent 121 transplantations performed within 6 months of listing. The 33 patients in the left upper quadrant would have been favored by the “MELD-Na” over those in the right lower quadrant, who receive higher priority under the current system.

Discussion

In 1956, the late Dame Sheila Sherlock observed, “In patients with liver disease, serum-Na levels below 130 mEq/L must be regarded as serious and, if below 125 mEq/L, ominous.” Her insight has been substantiated by a number of subsequent investigations that documented the importance of serum Na as a prognostic indicator in patients with cirrhosis. Because serum Na is a readily available, reliable, reproducible, and objective parameter, it represents a reasonable candidate for inclusion in a liver allocation model. In this work, we provide an evidence-based proposal for incorporating serum Na into the MELD, the current prioritization model for allocation of deceased donor liver grafts in the United States.

The main strength of this analysis is that the data were collected prospectively with a specific purpose of refining and validating the MELD from centers located in geographically diverse regions of the United States. In addition, only patients who were registered on the waiting list under the current allocation system based on the MELD were included in the analysis, which makes the data most applicable in waiting list patients today. The main points of this paper are (1) that findings of prior single center retrospective studies reporting an association between hyponatremia and waiting list mortality was confirmed; (2) that the development of a new model, “MELD-Na,” incorporating serum Na into the MELD was illustrated; and (3) that the potential impact of implementation of the “MELD-Na” for liver graft allocation was evaluated.

First, serum Na was strongly associated with risk of waiting list mortality, independent of the MELD score. After controlling for the MELD, for serum Na between 120 and 135 mEq/L, there was an inverse linear relationship between serum Na and mortality risk. It is thought that serum Na may reflect the risk of mortality in patients with persistent ascites in whom the MELD may underestimate their risk of death. A prior study by Heuman et al found that in patients with MELD score <21 and persistent ascites, hyponatremia was associated with an increased waiting list mortality. In a recent study from Argentina, ascites was present in all patients with hyponatremia, defined as Na <130 mEq/L. In the current analysis, only 11% patients with ascites also had hyponatremia, and thus, ascites was not sufficient to explain the excess mortality risk associated with hyponatremia. Based on these data, one may construe that in
the cascade of events leading to refractory ascites and hepatorenal syndrome in persons with portal hypertension, hyponatremia may represent an earlier or more sensitive pathophysiologic marker than increasing serum creatinine.\(^7\)

Second, the new model, “MELD-Na,” incorporates serum Na into the MELD using serum Na as a linear function for values of serum Na between 120 and 135 mEq/L. In Figure 3, the effect of serum Na on mortality after adjusting for the MELD had an inverse S shape with the highest risk of death in patients with low serum Na. Out of a number of cutoff values for the lower and upper limits of serum Na, those of 120 and 135 mEq/L, respectively, were chosen for clinical rationale as well as statistical justification as explained above. Another potentially important reason to impose a lower limit of serum Na among liver transplant candidates is the potentially devastating neurologic sequelae associated with low serum Na concentrations. For example, rapid normalization of serum Na in patients with severe hyponatremia who undergo liver transplantation may lead to central pontine myelinolysis.\(^20\)–\(^22\) Thus, an organ allocation system that heavily favors severely hyponatremic patients may potentially result in an increasing number of patients with neurologic problems following liver transplantation. A counterargument may be that it is the responsibility of the individual transplant physicians and surgeons to assess whether the patient is at too high a risk to undergo transplantation, a decision not uncommonly made in patients with an extremely high MELD score. Nonetheless, in our opinion, it is justifiable to establish specific lower and upper limits in serum Na for the purpose of organ allocation.

We also examined whether there is a need to adjust the coefficients for the individual components of the MELD. One may expect that the importance of creatinine may be diminished when Na is introduced because both creatinine and Na may be construed to reflect the renal function. However, 95% CIs from the current data set overlapped with the best fitting coefficients (point estimates) for the original MELD coefficients. The MELD coefficients were kept intact because numerous previous studies have validated the current MELD model.

In our evaluation of the potential impact of using the “MELD-Na”–based allocation system instead of a MELD-based system, we estimated that, with current graft availability, up to 27% of grafts could be redirected to patients on the waiting list favored by the “MELD-Na” score. Indeed, grafts would be redirected to patients at greater risk of mortality as indicated by the MELD combined with Na levels. Data in Figure 6 suggest that, if organ allocation is switched from the MELD to the “MELD-Na”–based system, the point necessary to receive transplantation will increase modestly (eg, from 18 to 22). Thus, under the new system, a patient with serum Na of 130 mEq/L and a MELD score of 14 will have a “MELD-Na” score of 22 and will be allocated an organ, whereas another patient with serum Na of 135 mEq/L and a MELD score of 20 (“MELD-Na” score of 20) will be given a lower priority. Obviously, the latter patient with a higher MELD score is being given a higher priority under the current system. Thus, this analysis suggests that the implementation of a “MELD-Na”–based organ allocation would result in an overall small increase in the score necessary for the patient with normal Na levels to receive priority for a transplant, whereas a significant number of patients with low serum Na will benefit by receiving a priority score corresponding to their mortality risk.

Third, the prior study by Heuman et al found that the association between hyponatremia and waiting list mortality was restricted to patients with a MELD score < 21 and persistent ascites.\(^23\) Our analysis also suggests that the effect of hyponatremia may be smaller in patients with high MELD scores than in those with lower MELD scores. Intuitively, there may be a level of the MELD score above which the risk of death represented by the MELD score alone is so high that even very low levels of serum Na no longer confer further mortality risk. However, because of the small number of patients with a high MELD score and low serum Na, we were unable to draw a firm conclusion on this point.

This consideration of an interaction between the MELD and serum Na (ie, whether the effect of serum Na may vary at different MELD levels) is potentially highly important because liver transplantation nowadays is commonly performed at MELD scores of upper 20s or higher. Thus, if the cutoff MELD score above which serum Na no longer contributes is lower than these, the introduction of serum Na will not alter the organ allocation in practice. Furthermore, whatever MELD cutoff score is used, there will be patients near the cutoff value whose priority will change dramatically by their serum Na. This issue of the interaction between the MELD score and serum Na needs to be carefully analyzed using a much larger data set with a large number of patients with low serum Na and high MELD scores. If a definite interaction is found, a graduated decrease in the effect of serum Na, rather than an abrupt cut off, will be necessary to avoid cumbersome shifting of allocation priorities in patients at the margin.

In spite of the useful conclusions that may be drawn from the analysis, this study has limitations. First,
although ascites was a problem commonly recognized in our cohort (reported in 62% of patients at the time of listing), we must point out that we used an inclusive definition of ascites (ie, any ascites detected clinically). Thus, the definition may have differed from one center to the next and, even within the same center, from one evaluator to another. This variability in definition may have been the reason that we found no association between ascites and waiting list mortality. As widely recognized, this is an inherent problem in the assessment of subjective parameters. Second, our study cohort was drawn from 5 academic liver transplantation centers, each with somewhat disparate patient populations, practice patterns, and availability of liver grafts. Recognizing this variability, we made sure that all of the models presented in this analysis were adjusted for center. However, such a statistical adjustment does not necessarily guarantee the generalizability of the conclusions. Third, although our study was based on a cohort of a reasonable size, the number of deaths that occurred during the observation was not sufficient to provide all of the information that is necessary to obtain concrete recommendations for implementation of the “MELD-Na.” For example, because of the limited number of deaths, we chose to model death within 6 months rather than 3 months as in our MELD validation study. Last, in our analysis, serum Na data were only available at the time of listing. Patients, particularly those with ascites, may develop hyponatremia while on the list. Thus, analyses limiting the time frame of the analysis to periods shorter than 6 months, or utilizing serum Na data subsequent to waiting list registration, may find that the effect of serum Na might be larger than was found in this analysis. However, it may also be worthwhile to point out that, in our experience, adding acuity in changes in the MELD did not substantially improve the performance of the MELD in predicting waiting list mortality. The same may hold for serial Na data, but for the lack of serial Na data, this analysis could not address the issue.

Because of these limitations of this and previous work by others, we believe and recommend that, ultimately, data collected by the United Network for Organ Sharing be analyzed to validate and finalize the details of the model, before adopting serum Na in organ allocation. In that context, this current analysis provides a road map for issues to be considered in future analyses. Based on the insight gained in this analysis, specific issues that may best be addressed using a national data set include (1) whether model coefficients for bilirubin, INR, and creatinine could be retained the same as in the MELD or need to be refit; (2) how to incorporate an interaction, if any, between the MELD and serum Na; and (3) whether using outcome for a shorter time frame strengthens the significance of serum Na.

For patients waiting for liver transplantation, the means by which these lifesaving organs are allocated is of paramount importance. As patient advocates, transplant physicians and surgeons are obligated to continue vigilance in their attempt to optimize our allocation models. We have developed a practical and evidence-based model, “MELD-Na,” that incorporates serum Na concentration into the MELD to improve prediction of liver transplant waiting list mortality. Although further refinement and validation are necessary, implementation of the “MELD-Na” for liver allocation may better identify those patients with the greatest medical urgency for transplantation.

References


Received May 20, 2005. Accepted January 25, 2006.
Address requests for reprints to: W. Ray Kim, MD, Division of Gastroenterology and Hepatology, 200 1st Street SW, Rochester, Minnesota 55905. e-mail: kim.ray@mayo.edu; fax (507) 538-3974.
Supported by grants from the National Institute of Diabetes, Digestive and Kidney Diseases (DK-34238 and DK-61617).