

Retransplantation for Hepatitis C: What Do We Really Know?

James R. Burton, Jr. and Hugo R. Rosen

You can know the name of a bird in all the languages of the world, but when you're finished, you'll know absolutely nothing whatever about the bird . . . so let's look at the bird and see what it's doing—that's what counts. I learned very early the difference between knowing the name of something and knowing something.

—Richard Feynman (1918–1988)

Hepatitis C virus (HCV) is the leading indication for liver transplantation (LT) worldwide. After transplantation, HCV recurrence is nearly universal, with up to 20–40% developing allograft cirrhosis after only 5 years.^{1–4} Effective therapies to eradicate the infection after transplantation or to prevent severe recurrence are lacking.^{5–7} Once cirrhosis develops, up to 2 / 3 will develop decompensation after 3 years; once decompensation develops, survival is very poor, with only 10% surviving 3 years.⁴ For many patients, retransplantation (re-LT) is the only option.

In general, re-LT has a lower survival rate than primary LT, and some studies have suggested that re-LT outcomes for HCV may be worse than those for non-HCV diagnoses.^{8–10} At least 15 studies have evaluated prognostic criteria associated with re-LT.¹¹ Factors identified in these studies as associated with poor outcome have included time to re-LT, United Network for Organ Sharing status, recipient age, renal dysfunction, hyperbilirubinemia, and most recently, model for end-stage liver disease (MELD). Most of our knowledge in the area of re-LT has come from single-center experience or has been derived from registry (e.g., United

Network for Organ Sharing) data. The article by Neff et al.¹² in this issue of *Liver Transplantation* is the latest article to examine factors associated with survival after re-LT, but the first to examine physical condition as a prognostic criteria.

Neff et al.¹² analyzed their experience with re-LT at the University of Miami and University of Cincinnati between July 1996 and February 2002. Retransplanted patients were divided into 2 groups, based on diagnosis before primary LT: HCV (group 1) and non-HCV (group 2). The study focused on re-LT for allograft dysfunction (AD), which is defined as graft dysfunction with persistent jaundice (>30 days) beginning at least 6 months after primary LT in the absence of other causes, such as vascular or biliary complications, infections, or medication-associated cholestasis. Though not statistically significant, more patients were retransplanted for AD in the HCV group than in the non-HCV group. The authors do not specify the cause of AD (i.e., recurrent HCV, chronic rejection) in those patients retransplanted with primary diagnoses of HCV. There were no significant differences between the groups in terms of days to re-LT, Child-Turcotte-Pugh (CTP) or MELD scores, and physical condition of those undergoing re-LT for AD. Of those with retransplant diagnoses of AD, 1-year graft survival rates were worse for those with HCV diagnoses compared to non-HCV diagnoses (50 vs. 75%, respectively; $P = .04$). Overall 1-year mortality rates between the groups were not significantly different, but trended to worse survival in the HCV group (45 vs. 67%, respectively). By using multivariate regression analysis, only physical condition at time of re-LT was found to be predictive of retransplant survival. Other factors such as total bilirubin, creatinine, CTP and MELD scores, donor age, and cold ischemia times were not found to be significant predictors of mortality. Because the study was underpowered to assess the predictive value of MELD, an alternative approach would have been to perform analysis of MELD groups instead, i.e., as a categorical variable instead of continuous variable.

Unlike any other study to date that has evaluated prognostic criteria with re-LT, this article assesses physical condition using a scale adapted from the American Society of Anesthesiologists' Physical Scale Classifica-

Abbreviations: HCV, hepatitis C virus; LT, liver transplantation; re-LT, retransplantation; MELD, model for end-stage liver disease; AD, allograft dysfunction; CTP, Child-Turcotte-Pugh.

From the Division of Gastroenterology / Hepatology, Oregon Health & Science University and Portland Veterans Administration Medical Center, Portland, OR.

Address reprint requests to James R. Burton, Jr., MD, Assistant Professor of Medicine, Oregon Health & Science University, 3181 SW Sam Jackson Park Road, PV-310, Portland, Oregon 97239. Telephone: (503) 494-8577; FAX: (503) 494-7556; E-mail: burtonj@ohsu.edu

Copyright © 2004 by the American Association for the Study of Liver Diseases

Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/lt.20325

tion (1 being the best score; 4 the worst). This scale was first devised in 1941 for the purpose of assessing the physical status of patients undergoing anesthesia.¹³ (Of note, the physical classification system used by the American Society of Anesthesiologists today is vastly different.¹⁴) The scale used in the study takes into account subjective complaints of fatigue by the patient, ability to perform activities of daily living, employment status, and whether the patient is living at home or hospitalized prior to retransplantation. It has not been validated, within the context of this study or in general, in patients with liver disease. As this was a retrospective chart review, classification bias may have played a large factor in this study. In addition, as the reviewers were not blinded to the diagnosis of the patient, bias may have played a role in the assignment of the physical condition level. Though not statistically significant, the group of patients with HCV had higher physical condition scores compared to the non-HCV group, despite similar CTP and MELD scores. The use of interferon-based therapy may explain this difference, as 27% of patients were on interferon-based therapies at the time of re-LT, which would certainly have contributed to fatigue and inability to work, and would possibly have contributed to hospitalization due to medication-related side effects that would not have been seen in the patients without diagnosis of HCV. Also, since this study included patients undergoing re-LT before implementation of the MELD system, those patients who were hospitalized (theoretically, those with higher physical condition levels) would have received higher priority for transplantation and thus may have been transplanted more frequently. What impact this had in this study is not clear, and in fact, not likely to be teased out with such a relatively small study size.

The use of physical condition assessment may already be in use today, though not formally, during the evaluation of patients for re-LT. It is likely that many transplant hepatologists and surgeons would have significant reservations about retransplanting a patient who is bedridden and / or hospitalized at time of re-LT for liver failure accompanied by malnutrition, fatigue, and deconditioning. In addition, this study reveals the physical condition scores of only those who underwent re-LT. We do not have data on how many patients were declined re-LT listings and how many died awaiting re-LT. Could a separate allocation system for re-LT incorporating physical conditioning be utilized? Given that the CTP-based allocation system was abandoned because it was too subjective, it is unlikely that a subjective factor like physical conditioning will be useful as a prognostic indicator for re-LT. Although we can say

that a physical condition level 2 is worse than level 1, we don't know how much worse this level is from level 3 or 4. In our transplant unit, we use a similar "eyeball" test, usually dichotomized into the patient "does or does not eyeball well."

An important observation from this study deserves to be mentioned. The HCV group and the non-HCV group underwent re-LT at nearly identical MELD scores (21.7 and 20.9, respectively), yet for the HCV group, this MELD score was associated with a 1-year survival rate of only 45%. This survival rate is much lower than would be expected for a MELD score of ~20, as reported by Watt et al.,¹⁵ but it illustrates the importance of considering survival in allocating organs to these patients. Awarding re-LT candidates additional MELD points, to allow re-LT at a lower biological MELD score, may be a way to improve survival. Doing so would require defining acceptable survival after re-LT for HCV. Edwards and Harper¹⁶ recently reported that the concordance of pre-LT MELD scores with graft failure at 90 days was poor for both primary and repeat transplants, suggesting that factors other than those used in calculating the MELD score play a role in determining early success of liver transplants. Neff et al.¹² describe their current approach to evaluating the most successful re-LT candidate with HCV. Admittedly hypothetical (and personally confusing, as it involves 4 factors in 2-dimensions), their approach involves a prognostic grid including HCV factors (i.e., high viral load, genotype 1, nonresponse to interferon, and intolerance to antiviral therapy), total bilirubin, serum creatinine, and their finding of physical conditioning. The concept of identifying high-risk candidates for re-LT is an important one that deserves further evaluation. Unfortunately, at the present time, precisely which factors and what levels provide discriminant prediction are unknown.

This study does not help resolve our lack of knowledge about re-LT outcome. Re-LT survival is undoubtedly impacted by a number of donor, recipient, and surgical variables. This past year, a Retransplant Study Group was established, whose aims are as follows: to compare patient and graft survival after re-LT (in patients with graft failure due to recurrent HCV) with other indications for re-LT; to identify patient, donor, and clinical variables associated with poor survival; and to develop survival models for re-LT. Another important aim of this Study Group will be to identify: how many patients with recurrent HCV cirrhosis are considered for relisting; how many are declined relisting; the reasons they are declined relisting; and of those relisted, how many died prior to re-LT. Hopefully, this

will be the first step toward development of uniform guidelines that will assist in the management of these very challenging patients.

References

1. Gane E. The natural history and outcome of liver transplantation in hepatitis C virus-infected recipients. *Liver Transpl* 2003;9: S28–S34.
2. Fattovich G, Giustina G, Degos F, Diodati G, Tremolada F, Nevens F, et al. Effectiveness of interferon alfa on incidence of hepatocellular carcinoma and decompensation in cirrhosis type C. *J Hepatol* 1997;27:201–205.
3. Kenny-Walsh E. Clinical outcomes after hepatitis C infection from contaminated anti-D immune globulin. *Irish Hepatology Research Group. N Engl J Med* 1999;340:1228–1233.
4. Berenguer M, Prieto M, Rayon JM, Mora J, Pastor M, Ortiz V, et al. Natural history of clinically compensated HCV-related graft cirrhosis following liver transplantation. *Hepatology* 2000; 32:852–858.
5. Gopal DV, Rabkin JM, Berk BS, Corless CL, Chou S, Olyaei A, et al. Treatment of progressive hepatitis C recurrence after liver transplantation with combination interferon plus ribavirin. *Liver Transpl* 2001;7:181–190.
6. Narayanan Menon KV, Poterucha JJ, El-Amin OM, Burgart LJ, Kremers WK, Rosen CB, et al. Treatment of posttransplantation recurrence of hepatitis C with interferon and ribavirin: lessons on tolerability and efficacy. *Liver Transpl* 2002;8:623–629.
7. Stravitz RT, Shiffman ML, Sanyal AJ, Luketic VA, Sterling RK, Heuman DM, et al. Effects of interferon treatment on liver histology and allograft rejection in patients with recurrent hepatitis C following liver transplantation. *Liver Transpl* 2004;10: 850–858.
8. Rosen HR, Martin P. Hepatitis C infection in patients undergoing liver retransplantation. *Transplantation* 1998;66:1612–1616.
9. Biggins SW, Beldecos A, Rabkin JM, Rosen HR. Retransplantation for hepatic allograft failure: prognostic modeling and ethical considerations. *Liver Transpl* 2002;8:313–322.
10. Yoo HY, Maheshwari A, Thuluvath PJ. Retransplantation of liver: primary graft nonfunction and hepatitis C virus are associated with worse outcome. *Liver Transpl* 2003;9:897–904.
11. Burton JR Jr., Sonnenberg A, Rosen HR. Retransplantation for recurrent hepatitis C in the MELD era: maximizing utility. *Liver Transpl* 2004;10:S59–S64.
12. Neff GW, O'Brian CB, Nery J, Shire NJ, Nishida S, de la Garza J, et al. Factors that identify survival following liver retransplantation for allograft failure due to recurrent hepatitis C infection. *Liver Transpl* 2004;10:1497–1503.
13. Saklad M. Grading of patients for surgical procedures. *Anesthesiology* 1941;2:281–284.
14. American Society of Anesthesiologists. Physical Status Classification System. <http://www.asahq.org/clinical/physicalstatus.htm>. Accessed October 3, 2004.
15. Watt KDS, Lyden ER, McCashland TM. Poor survival after liver transplantation: is hepatitis C to blame? *Liver Transpl* 2003;9: 1019–1024.
16. Edwards E, Harper A. Does MELD work for relisted candidates? *Liver Transpl* 2004;10:S10–S16.