Controversies in Liver Transplantation for Hepatitis C

Hepatitis C is one of the most common indications for liver transplantation in the United States, accounting for approximately 40%–45% of all liver transplants. Unfortunately, recurrent disease is universal in patients who are viremic before transplantation. This can lead to cirrhosis in at least 25% of patients 5 years after liver transplantation, and recurrent hepatitis C is now emerging as an important but occasionally contentious indication for retransplantation. Several attempts have been undertaken to identify patients at high risk for severe recurrent disease who may benefit from treatment, but unfortunately antiviral therapy frequently is ineffective and often is associated with numerous side effects. Although we have made significant strides in understanding the natural history of this disease in non-transplant patients, this does not hold true for the transplant population in which several uncertainties covering virtually the entire spectrum of liver transplantation persist. Despite these concerns, on a more practical level, it is usually only in the postoperative setting that clinicians truly can assess the impact of their interventions on the natural history of recurrent hepatitis C, for example, by adjusting immunosuppression or prescribing antiviral therapy. Preoperative and perioperative (including donor) factors often are outside the control of hepatologists and transplant surgeons. This review is not an inclusive review of the literature but summarizes what we believe are the more controversial topics of this disease.

Since liver transplantation (LT) was approved as a life-saving intervention for end-stage liver disease in 1983, decompensated cirrhosis from hepatitis C virus (HCV) has become the leading indication for LT in the United States. Over the past decade several studies have reported that short- and long-term outcomes of LT for HCV are poorer compared with LT for non–HCV-related diseases, including patients transplanted for hepatocellular carcinoma. This is in large part owing to the universal recurrence of HCV as well as synergistic cofactors that influence disease progression (Table 1).

It is widely recognized that cirrhosis from recurrent HCV occurs in at least 25% of patients within 5 years of transplantation with an annual risk of decompensation of 42% once cirrhosis has developed. These dismal statistics highlight the importance of recurrent HCV, which in turn stimulated the controversy surrounding retransplantation of recurrent HCV. It would appear intuitive that eradicating HCV either before LT or treating recurrent HCV shortly after LT would have a major impact on decreasing the incidence of recurrent HCV and its attendant complications. Unfortunately, most patients referred for LT evaluation have decompensated cirrhosis and frequently are unable to tolerate pegylated interferon and ribavirin therapy. The treatment of recurrent HCV is complicated further by poor sustained viral response (SVR) rates and reports of progressive fibrosis with hepatic decompensation despite SVR. Perioperative factors such as transport injury and donor factors such as advanced age and steatosis also have a negative impact on the severity of recurrent HCV. The most successful approach to the treatment of recurrent HCV remains eradicating HCV before hepatic decompensation in which reported SVR rates with pegylated interferon and ribavirin vary from 50% to 70%. However, this will necessitate a paradigm shift in the treatment of HCV. Most clinicians are comfortable in treating HCV before transplantation, but the added dimension of the posttransplant period with the confounding variables of immunosup-
operative factors.

perioperative (including donor-related factors), and post-

have divided this article into 3 sections: preoperative,

Pretransplant factors
High HCV-RNA level
Recipient ethnicity (non-Caucasians do worse)

Donor factors
Advanced age

Posttransplant factors
T-cell–depleting therapies
Inappropriate treatment of Banff A1 ACR with steroid boluses
Cytomegalovirus disease
Year of transplantation (worse with recent transplants)

Table 1. Factors Associated With Poor Outcomes in LT for Recurrent HCV

Pretransplant factors
High HCV-RNA level
Recipient ethnicity (non-Caucasians do worse)

Donor factors
Advanced age

Posttransplant factors
T-cell–depleting therapies
Inappropriate treatment of Banff A1 ACR with steroid boluses
Cytomegalovirus disease
Year of transplantation (worse with recent transplants)

Pressor drugs and abnormal hematologic, infectious,
and liver function parameters deter all but the most
determined and confident. This article is not an inclusive
review of the literature of LT surrounding liver transplan-
tation and HCV but focuses on what we believe are the
more controversial topics of this disease (Table 2). We
have divided this article into 3 sections: preoperative,
perioperative (including donor-related factors), and post-
operative factors.

Preoperative Factors

Treatment of Hepatitis C in Decompensated Cirrhotic Patients

Since a landmark study reported high HCV-RNA
levels before LT negatively impact survival after LT,2
there have been several attempts to eradicate HCV in
decompensated cirrhotic patients pretransplant, a pa-
tient population in whom antiviral therapy is generally
considered contraindicated. Three recent studies have
reported mixed results in this high-risk group of patients.
Crippin et al3 conducted a randomized trial of interferon
with and without ribavirin in 15 patients with decomp-
sensated cirrhosis at or near the top of the waiting list.
Although 33% of patients achieved loss of HCV RNA on
treatment, 20 serious adverse events occurred, including
2 infective complications. One patient developed septic
arthritis that responded to antibiotics and the other
developed culture-negative empyema that progressed to
multiorgan failure and death. Everson et al4 treated 124
decompensated cirrhotic patients with a low accelerating
dose regimen of either interferon alfa-2b or pegylated
interferon alfa-2b with ribavirin and reported an SVR of
24%. Close inspection of the data revealed a majority
(45%) of patients were Childs–Turcotte–Pugh class A,
49% of non–genotype 1 patients were Childs–Turcotte–
Pugh class C, and only 13% of genotype 1 patients
achieved a post-LT SVR. Fifteen patients with genotype 2
or 3 disease underwent LT of whom 9 were HCV-RNA
negative pre-LT but 2 relapsed, which translates to a
post-LT SVR of 50%. This suggests that unlike the poor
outcomes associated in patients with genotype 1 disease,
a more aggressive approach to patients with genotype 2
and 3 may be reasonable, particularly because a shorter
duration of therapy may be sufficient and assessing re-
sponse to therapy occasionally can be determined after 4
weeks of treatment. The recent study by Martinez–Bauer
et al5 was unique because the treatment regimen con-
sisted exclusively of pegylated interferon and ribavirin in
50 cirrhotic patients with HCV on the LT waiting list.
The baseline model for end-stage liver disease (MELD)
score was 12, with Childs–Turcotte–Pugh score and HCV
genotype distribution similar to Everson’s study. Of the
46% of patients who became HCV-RNA negative before
transplantation, a post-LT SVR of 71% and relapse rate of
29% was reported. Further analysis of the data showed
only 20% of genotype 1 patients maintained post-LT
SVR. Side effects included life-threatening complications
such as hepatic decompensation and infection (32%),
neutropenia (20%), and 2 deaths on therapy attributable
to spontaneous bacterial peritonitis.

Based on these studies, treatment of decompensated
genotype 1 cirrhotic patients with combination therapy
appears questionable because adverse effects are common
with post-LT SVR rates of 24%, a result comparable with
the SVR achieved post-LT but without the associated
morbidity or potential mortality. Patients with the most
advanced decompensated liver disease may have the most
to gain from viral clearance with interferon but have the
least reserve for recovering from life-threatening infec-
tions aggravated by cytopenias from interferon. The risks
of antiviral therapy in this group appear to outweigh the
benefits and should be undertaken only under the aus-
pices of a clinical trial or a closely supervised academic
setting.

Liver Transplantation in HCV–Human Immunodeficiency Virus Co-Infected Patients

Since the introduction of highly active antiretro-
viral therapy, co-infected patients with human immuno-

Table 2. Controversial Topics in LT for HCV

Preoperative factors
Antiviral therapy in decompensated cirrhotic patients
Evaluation of HIV/HCV co-infected patients for LT
Listing for LT and KT in decompensated cirrhotic patients with hepatorenal syndrome

Donor factors
HCV status
Older donors

Perioperative factors
Impact of preservation injury on recurrent HCV

Postoperative factors
Immunosuppression induction and maintenance
Steroids
Treatment of recurrent HCV in liver and liver–kidney transplant recipients
Living donor vs deceased donor outcomes
Recurrent HCV and DM
Differentiating recurrent HCV from rejection
Interferon and risk of hepatic allograft rejection
Monitoring disease progression and role of protocol biopsies
Retransplantation
syndrome with dialysis dependency is present for at least 8 weeks, although several authorities recommend an even shorter period of dialysis before listing. An alternative approach is to consider sequential LT followed by kidney transplantation (KT) for those patients with hepatorenal syndrome of less than 8 weeks duration without evidence of intrinsic kidney disease who remain dialysis-dependent after LT. This strategy seems reasonable because recurrent HCV is universal after LT and if simultaneous LT–KT is performed, these patients cannot be treated for recurrent HCV with interferon-based therapies without an unacceptably high risk of precipitating renal allograft rejection. There are reports of increased complications of sequential KT in LT recipients with HCV. However, this approach in patients with short-term (<8 weeks) hepatorenal syndrome who may have reversible renal failure potentially precludes combined LT–KT, thereby saving a valuable organ from the limited kidney donor pool but also allows treatment of recurrent HCV in the liver recipient.

**Donor Factors**

*Are Outcomes Improved in Recipients Who Receive HCV-Positive Donors?*

The role of extended-criteria donors and donation after cardiac death donors has gained broader acceptance in the LT community, although studies evaluating long-term outcomes in HCV recipients are lacking. One of the more controversial issues regarding extended-criteria donors revolves around the potential positive impact of HCV-infected donors on short-term outcomes. Wilson et al performed a case-control study using data from the United Network for Organ Sharing and local donor data to identify 38 HCV-infected recipients of HCV-infected livers. The outcomes were compared with those of 76 liver transplant recipients of donor livers meeting strict United Network for Organ Sharing criteria. Demographics were similar between the extended criteria donor group and the standard matched donor recipients. Warm and cold ischemia times also were similar. Interestingly, 1-year patient survival rates of 97% favored recipients of HCV-infected livers compared with 1-year patient survival rates of 87.5% for recipients of organs meeting United Network for Organ Sharing criteria. A 26% increase in fibrosis developed in HCV-infected organs at 1-year posttransplant compared with a 69% increase in fibrosis in the United Network for Organ Sharing-approved group. The findings of this study have important implications because such organs are underused but overrepresented in the donor pool. If the results of this study are validated by others, we will have come full circle regarding the use of HCV-positive liver donors from initial hesitation to a full embrace.

### Table 3. Criteria for Listing for HCV/HIV Co-Infected Patients

| Meet criteria for liver transplantation | Documented HIV infection by licensed enzyme-linked immunosorbent assay and confirmation with Western blot or history of detectable HIV RNA |
| CD4 cell count >100/μL in the 16 weeks before LT | If patient is on antiretroviral therapy, HIV RNA <50 copies/mL if Amplicor Monitor Ultrasensitive polymerase chain reaction assay used or <75 copies/mL if branched DNA Versant version 3.0 assay used |
| Patients with a history of certain opportunistic infections or malignancies may be considered (further details on www.HIVTransplant.com) | |

Amplicor Monitor (Roche, Nutley, NJ); Versant (Bayer Diagnostics, Berkeley, CA).
Should Older Donors (>60 Years) Be Used in HCV-Positive Recipients?

The impact of donor age on outcomes has gained increasing importance because of the increased use of livers from older donors, reflecting the increasing imbalance between organ supply and demand. A recent study reported older allografts were at greater risk for the most severe histologic features and decreased survival compared with younger allografts \( (P < 0.02 \text{ for all outcomes}) \) using Cox proportional hazards analysis. In their elegant study on the development of a quantitative donor risk index using data from 20,023 transplants performed in the United States between 1998 and 2002, Feng et al\(^1\) reported that of the 7 donor characteristics associated with poorer outcomes, donor age older than 60 years of age was the strongest risk factor for graft failure (relative risk, 1.53) in contrast to younger donors. However, their model was adjusted for hepatitis C status and showed that regardless of the cause of liver disease, the use of donors older than 60 years of age was associated with poorer outcomes. However, it remains difficult if not impossible to define an age cut-off level when older donors should not be used; we only have the liberty of making such statements when organ supply exceeds demand. Until we reach that stage we need to examine the interaction between donor risk index and recipient risk factors using national data and, although candidates who are most ill may have disproportionately poorer outcomes with higher-risk grafts, this interaction has yet to be defined fully outside modeling studies.\(^1\)

Postoperative Factors

Immunosuppression

The ideal immunosuppressive regimen during the transplant process is unclear despite several advances in our understanding on the impact of various medications on HCV recurrence in parallel with the development of promising new drugs. We have divided this topic into the following sections: induction therapy, maintenance therapy, and the role of maintenance steroids.

Induction Therapy

Antithymocyte globulin. Because OKT3 and alemtuzumab have been associated strongly with severe recurrent HCV, several alternative regimens have been proposed for induction, although it remains uncertain which combination will have the dual effects of preventing graft rejection and decreasing the risk of severe recurrent HCV.\(^19,20\) The use of rabbit antithymocyte globulin (ATG) as part of a steroid-free protocol gained increasing popularity when an early randomized controlled trial showed a reduced incidence of recurrent HCV in ATG patients (50\%) vs steroid bolus recipients (71\%), although this difference was not statistically significant.\(^21\) These encouraging findings led to widespread use of ATG and as of September 2007, at least 8 centers have reported their experience with rabbit ATG without steroids vs steroid induction for recurrent HCV. The results are conflicting, with several centers reporting a higher incidence of acute rejection in non-ATG patients and others stating ATG had no impact on graft or patient survival.\(^22,23\) The interpretation of these various studies is clouded further by the different regimens used for maintenance immunosuppression, which can influence the course of recurrent HCV. At present, there are no data that conclusively show that ATG has a positive impact on HCV recurrence in comparison with steroid induction.

Anti-CD antibodies: basiliximab and daclizumab.

There have been only a handful of trials evaluating the impact of monoclonal antibodies for induction in LT and even fewer in recurrent HCV. Filipponi et al\(^24\) randomized 140 patients to basiliximab and steroids or basiliximab and placebo followed by cyclosporine and azathioprine in both groups in which the primary end point was histologic recurrence of HCV (defined as an Ishak score >18) at 12 months. The histologic recurrence rate was 41.2\% with basiliximab and steroids vs 37.5\% with basiliximab and placebo \( (P = .354) \) together with a lower treatment failure rate in the steroid-free group. Klintmalm et al\(^25\) recently reported results of a 2-year prospective randomized study evaluating the impact of immunosuppression on recurrent HCV progression and incidence of rejection. Recurrent HCV was defined as the presence of at least grade 3 inflammation or at least stage 2 fibrosis in liver biopsies performed within the first year according to the classification described by Batts and Ludwig. The investigators randomized 312 patients to 3 arms: arm 1 \( (n = 80) \): tacrolimus plus prednisone; arm 2 \( (n = 79) \): tacrolimus plus prednisone plus mycophenolate mofetil (MMF); arm 3 \( (n = 153) \): daclizumab plus tacrolimus plus MMF. Protocol biopsies were performed at 90, 365, and 720 days. At the 2-year follow-up evaluation, there was no statistical difference in the incidence of rejection, HCV-RNA viremia, HCV recurrence, patient survival, or graft survival among the 3 groups. However, more accelerated HCV recurrence was observed between years 1 and 2 in arms 1 and 2. The investigators concluded that although HCV recurrence at 2 years was not influenced by immunosuppression, the rate of progression in year 2 may have been influenced by steroids and MMF and recommended longer-term follow-up evaluation for these patients.

Until adequately powered randomized controlled trials are performed, the use of monoclonal antibodies in LT should be used with caution and under the rigor of a clinical trial because there is insufficient evidence to recommend its use for induction. The long-term results of the follow-up evaluation from the study by Klintmalm et al\(^25\) will provide valuable data, but studies comparing ATG vs monoclonal antibodies also are awaited eagerly.
**Maintenance Therapy**

Calcineurin inhibitors. The impact of calcineurin inhibitors on the natural history of recurrent HCV has gained renewed interest after recent in vitro studies showing an antiviral effect of cyclosporine on HCV replication in the replicon system. This was supported by a retrospective study comparing cyclosporine with tacrolimus in patients who received interferon-based therapy for recurrent HCV. Patients treated with cyclosporine (46%) were more likely to achieve SVR vs patients treated with tacrolimus (27%) \( (P = .03) \). In addition, not only did cyclosporine inhibit HCV replication in a dose-dependent manner but when combined with interferon had an additive effect independent of interferon signaling. Although there was no statistically significant difference in patient survival between the 2 groups, cyclosporine-treated patients had a lower baseline HCV RNA and more episodes of acute cellular rejection requiring steroid treatment. These findings have not been reproduced in randomized, controlled prospective studies evaluating outcomes at 1 year post-LT. A recent meta-analysis reported similar rates of fibrosis and patient and graft survival at 1 year regardless of which calcineurin inhibitor was chosen. The diabetogenic impact of tacrolimus on the natural history of recurrent HCV remains a concern, although a recent study showed no difference in outcomes in cyclosporine vs tacrolimus-treated HCV patients at 3 years. Currently, a randomized controlled prospective study comparing cyclosporine vs tacrolimus incorporating serial liver biopsies and HCV-RNA levels is underway. At present, it seems reasonable to state that current evidence does not support a beneficial effect of cyclosporine over tacrolimus on HCV recurrence.

Azathioprine and MMF. Data on the impact of azathioprine and MMF on HCV recurrence has been at odds. A well-designed, randomized, prospective study of 106 patients comparing tacrolimus plus steroids vs tacrolimus plus steroids plus MMF showed no effect of MMF on patient or graft survival or HCV recurrence. However, subsequent studies, albeit smaller in size and nonrandomized, have reported worsening HCV RNA viremia upon either azathioprine substitution for MMF or when azathioprine is compared with MMF. Wiesner et al also recently reported that MMF was an important factor in improved outcomes in patients on tacrolimus-based immunosuppression after a multiple regression analysis of 11,670 patients reported to the Scientific Registry of Transplant Recipients. The wide spectrum of reported results is difficult to interpret but nonetheless a common factor in all the earlier-described studies is not whether MMF is superior to azathioprine but rather the overall intensity of immunosuppression may have more of an impact on HCV recurrence than the independent action of either drug.

**Rapamycin.** Rapamycin has gained widespread use in selected transplant programs as a maintenance agent because of its renal-sparing effects. Until results from well-designed, randomized trials are available there is little evidence to support its widespread role in recurrent HCV patients with renal dysfunction. The addition of MMF with lower doses of calcineurin inhibitors would appear to be more appropriate.

**Steroids.** Until 2002, steroids routinely were discontinued in most LT programs by 3 months because of the long-term side effects and prevalent belief that steroids increased HCV liver injury. However, a provocative, single-center, retrospective study of 80 patients by Brillanti et al reported slow steroid tapering was associated with less severe recurrent disease (defined as a modified Knodell score of ≤8) at 6 and 12 months. This was supported by Berenguer et al who compared outcomes between 2 cohorts of recurrent HCV patients; a group transplanted between 2001 and 2004 and a second group transplanted between 1999 and 2000 before dual immunosuppression (cyclosporine or tacrolimus plus steroids) or slow steroid taper over 6 months was instituted. This study was notable for the inclusion of annual liver biopsies with the study end point reported as the rate of bridging fibrosis, cirrhosis, or fibrosing cholestatic HCV at 1 year. Severe disease was considerably lower in the group transplanted between 2001 and 2004 (29% vs 48%; \( P = .02 \)). However, there were important limitations in this study, the most important being the use of historical controls that were not comparable with the 2001–2004 cohort. For example, year of transplantation has been reported by these investigators as an important risk in the development of recurrent HCV and may have accounted for these differences in outcome. Interestingly, the investigators also reported that the historical group from 1999 to 2000 were more likely to have received more intense immunosuppression and more steroid boluses, suggesting the beneficial effects of low-dose prednisone was confounded by a variety of historical factors, a theme common in many retrospective comparative studies.

The most compelling data to support low-dose steroids are from Vivarelli et al who recently reported the results of a randomized study of rapid (group A) vs slow steroid taper (group B) on 47 patients in conjunction with tacrolimus. At 1 year, 65% of patients in group A had histologic recurrence vs 75% in group B, with advanced fibrosis (stages 3 and 4) more common in the former (42% vs 7.6%; \( P = .03 \)). At the 2-year follow-up evaluation, advanced fibrosis-free survival was 60.8% in group A and 93.7% in group B \( (P = .03) \). This important article should hopefully resolve the controversy regarding the impact of low-dose steroids on the natural history of recurrent HCV. Given the well-known diabetogenic complications of steroids, particularly when tacrolimus is the primary immunosuppressive agent, the role of long-term steroid use remains an important question.
Does Recurrent HCV Increase the Risk of Developing Diabetes Mellitus?

Several studies have raised the possibility of an association between recurrent HCV and the development of new-onset diabetes mellitus (DM), which in turn can impact graft and patient survival. Other studies have failed to show such an association partly owing to the high prevalence of DM in the post-LT setting, regardless of the cause of liver disease, and the presence of confounding factors such as age, body mass index, race, sex and immunosuppressants, particularly steroids and tacrolimus, which increase the incidence of diabetes in both HCV-positive and HCV-negative patients. Comparing the incidence of DM between studies is frequently difficult because of methodologic differences in study design including the criteria for diagnosing DM. A causal relationship rather than an association between HCV and DM was strongly suggested by a study of 28,942 kidney transplant patients. When Cox proportional hazards regression models were used to calculate adjusted hazard ratios for the association of sero-pairs for HCV (donor positive/recipient negative, donor positive/recipient positive, donor negative/recipient positive, and donor negative/recipient negative) with Medicare claims for de novo post-LT HCV and post-LT DM, associations for both complications were significant in adjusted analysis. This strongly supported the concept that HCV increases the risk of DM. Growing evidence showing that HCV induces insulin resistance by a variety of mechanisms should alert clinicians to the importance of minimizing diabetogenic drugs in the transplant population in concert with aggressive diabetic control. The relative risk of developing DM in the presence of recurrent HCV is difficult if not impossible to calculate because of the absence of long-term prospective studies. Nonetheless, it is reasonable to infer the risk is not insignificant, associated with marked morbidity despite excellent short-term survival, and although long-term data are lacking, it is very likely that DM impacts patient and graft survival.

Differentiating Recurrent HCV From Mild/Moderate Rejection

Differentiating recurrent HCV from mild/moderate rejection continues to be a Sisyphean struggle, particularly in the first few months post-LT when the findings of recurrent HCV may be subtle, nonspecific, and overlap with features of acute cellular rejection (ACR). Although histopathology often is considered to be the gold standard for any diagnosis, this does not appear to hold absolutely true for recurrent HCV when mild or moderate rejection is in the differential diagnosis. To add complexity to the issue not only can both diseases coexist simultaneously, making diagnostic interpretation and management problematic, but no consensus has been reached as to what Banff score of rejection mandates steroid bolus or T-cell depleting therapy. Because the risks of inappropriate treatment of rejection with these medications are well known, this has led to clinicians and pathologists using clinical criteria such as time from LT, degree of immunosuppression, HCV-RNA levels, and extent of biochemical abnormalities to assist them in establishing a diagnosis rather than solely relying on histopathology.

The difficulty associated with arriving at the correct diagnosis is exemplified in the early (first 2–3 months) post-LT period when rejection traditionally has been viewed as a more common complication than recurrent HCV. Patients suspected of mild-moderate rejection when markedly increased liver tests and low therapeutic levels of immunosuppression are present are often treated with steroid boluses rather than watchful waiting with serial liver function tests and biopsies, the preferred option for patients outside this early time period. The efficacy or danger of increasing maintenance immunosuppression has on recurrent HCV or mild-moderate rejection in an effort to avoid steroid boluses has not been subject to clinical trials. Recent reports also have described recurrent HCV developing as early as 9 days post-LT in parallel with markedly increased HCV-RNA levels, which belies our current dogma that recurrent HCV is uncommon in the immediate post-LT period. This issue is complicated further in patients with severe preservation injury, a known risk factor for poor outcomes in recurrent HCV, in which histologic differentiation from fibrosing cholestatic HCV can be difficult.

Checking HCV-RNA levels in the early posttransplant period has historically been a potential predictor of identifying patients at high risk of recurrent HCV but instead may play an adjunctive role in the diagnosis of this disease process. However, its clinical utility may be dampened by the 48- to 96-hour delay in obtaining levels. In the late (>60 days) post-LT period, data on the utility of HCV-RNA levels for differentiating recurrent HCV from rejection remains mixed, although an excellent study cautions about diagnosing moderate rejection in patients with HCV-RNA levels exceeding 10 million IU/mL.

Although not currently in widespread use, ancillary investigations may play a pivotal role in the differentiation of these 2 conditions. Anti-HCV core titers were reported to increase in 82% of recurrent HCV cases in concert with an increasing ALT level, to stabilize or decrease in 100% of patients with acute cellular rejection, and to increase in 91% of doubtful cases that eventually were diagnosed as recurrent HCV. HCV-RNA serum levels did not fluctuate in these 3 groups. Grassi et al also reported that immunoperoxidase staining for HCV antigens may aid in the diagnosis of recurrent HCV although sensitivity and specificity were not provided. A positive result was strongly influenced by time from LT and a markedly positive test correlated with a poor response to antiviral therapy. However, when both rejection and recurrent HCV coexisted, the investigators were un-
able to clarify the role of HCV antigen staining to determine which was the predominant process. Schmeding et al. recently reported that C4d, a marker of complement activation and historically of more value in assessing humoral rather than cellular rejection, may have an important supportive role in distinguishing ACR from recurrent HCV with a sensitivity of 68% and a specificity of 90%. Sreekumar et al. reported that of 6412 genes analyzed, 25 were over expressed by more than 2-fold in patients with recurrent HCV and 15 were under expressed in acute rejection. Acute rejection was associated with over expression of genes associated with major histocompatibility complexes 1 and 2, T-cell activation, apoptosis induction, and insulin growth factor 1 and 2.

It is uncertain whether recurrent HCV increases the risk of developing ACR. Several studies have examined this association with conflicting results. In one of the earliest studies, Wiesner et al. reported an incidence of early (<6 wk) ACR in HCV of 52% in a multicenter study of 762 patients. This was corroborated by McTaggart et al. who reported an incidence of early (<6 mo) ACR in patients transplanted for HCV of 49%, comparable with rejection rates seen in autoimmune patients, a group often considered to be at higher than average risk of rejection. Interestingly, interferon treatment had no impact on the outcome of ACR in the study by McTaggart et al. An important limitation of both studies was the inability to unequivocally diagnose ACR from recurrent HCV owing to histologic ambiguity and possible selection bias. Present evidence does not support the concern that recurrent HCV increases the risk of ACR. The adverse consequences of steroid use on recurrent HCV demands caution in the treatment of suspected ACR.

**Recurrent HCV Treatment in Liver–Kidney Transplant Recipients**

Interferon-based therapies are virtually contraindicated in the presence of a renal allograft because of the unacceptable high risk of precipitating renal allograft rejection. This pool of patients is likely to increase because the number of patients with HCV undergoing combined LT–KT has increased since the introduction of MELD. Despite a lack of clinical trials, most transplant physicians do not treat KT or LT–KT recipients with pegylated interferon because of the fear that rejection will be precipitated, similar to standard interferon preparations. Although a recent case report described successful recurrent HCV eradication with pegylated interferon and ribavirin in an LT–KT recipient with no evidence of renal allograft dysfunction, the decision to use pegylated interferon and ribavirin can be made only on a case-by-case basis when the risks of progressive liver failure from recurrent HCV appear to outweigh the risk of renal allograft rejection from antiviral therapy. We would recommend periodic liver biopsies to determine the progression of liver disease and only consider treatment when the risk of liver allograft loss from recurrent HCV is greater than the risk of precipitating irreversible renal allograft failure from antiviral treatment.

**Treatment of Recurrent HCV**

The treatment of recurrent HCV is probably one of the most contentious topics in LT in part owing to the paucity of well-designed randomized studies despite the ubiquitous use of interferon and ribavirin in transplant centers since 1996. SVR is between 33% and 42% in randomized studies treating patients with histologic recurrence and 0% to 33% when used in a pre-emptive protocol. The use of hepatitis C immunoglobulins also has been disappointing in the prevention of recurrent HCV unlike the successes noted with hepatitis B immunoglobulin. Because SVR remains disappointingly low with both strategies, expert opinions suggest treating patients only with established disease in the presence of fibrosis and a bilirubin level of less than 3 mg/dL, but this is often not realistic for several reasons. Patients with recurrent HCV, markedly increased transaminase levels, and minimal fibrosis rarely are observed; instead they are subjected to frequent liver biopsies because the differential diagnosis of increased aminotransferases in a transplant patient is broad and not restricted to recurrent HCV. In such a circumstance a reasonable course would be that rather than performing repeated biopsies, a decision to treat with antiviral therapy from the outset may be reasonable. Liver biopsies often are prone to sampling errors and alternative methods for assessing progressive liver injury may be required. For those patients who develop fibrosing cholestatic HCV, the response to antiviral therapy usually is poor, but for the subgroup who do occasionally respond, no clear guidelines are available regarding how long treatment should be continued.

To add fuel to the fire, there also is evidence of progressive liver fibrosis after SVR eradication in patients treated with interferon-based therapies. In some instances this has led to decompensated cirrhosis requiring retransplantation in patients remaining serum HCV-RNA negative at a mean follow-up period of 18 months after LT. This complication calls into question what role, if any, do costly, frequently ineffective, and poorly tolerated antivirals have in the post-LT setting, particularly when progressive fibrosis and hepatic decompensation can develop despite sustained HCV eradication. This concern extends to the use of hematologic growth factors that often are used to treat the side effects of antiviral therapy, but despite their almost reflexive use, this has not translated into improved SVRs. Because these medications also are expensive and carry their own unique side effects, their universal use to treat the side effects of antiviral therapy needs to be examined closely and instead dose reduction should be the first option.

These concerns take a different twist when patients are retransplanted for recurrent HCV. A survey of 96 LT programs in the United States reported that although
only 60% of programs had a protocol for managing recurrent HCV after the first LT and 33% treat only patients with severe recurrence, 67% pre-emptively treat after retransplantation. The driving motivation most likely being the fact that these patients are unlikely to be retransplanted a third time for recurrent HCV and treatment, out of necessity, becomes empiric in the absence of data.

No two transplant centers are alike and neither are patients with recurrent HCV. The known limitations of antiviral therapy for recurrent HCV begs us to ask first and foremost whether treatment should even be considered (Table 4). Although this may sound heretical, transplant physicians need to strongly consider the risks vs benefits of treatment and consider this issue from the perspective of a patient who may rightly refuse treatment (on the grounds of low efficacy and side effects) or from perhaps an insurer who refuses to cover a possibly ineffective and prohibitively expensive treatment in the absence of cost-effectiveness data. For patients who refuse treatment, this should not lead to denial of retransplantation in the event of hepatic decompensation because they are refusing a treatment with a poor track record of success, not a life-saving intervention. Unlike the risks of renal allograft rejection with interferon—the risks of hepatic allograft rejection with interferon appear to be smaller but are not insignificant—careful monitoring of liver function tests while on interferon therapy and a low threshold for performing liver biopsy should be the standard of care.

### Does Interferon Increase the Risk of Hepatic Allograft Rejection?

Since interferon was first used for treating recurrent HCV more than 10 years ago, there have been concerns the risk of hepatic allograft rejection is increased. Although an early retrospective study on 105 patients treated with interferon did not show any such increase in rejection rates compared with a control group, the interferon-treated patients also received greater baseline immunosuppression. However, Stravitz et al reported that of 23 patients treated with interferon-based therapy for recurrent HCV, 8 (35%) had either acute or chronic rejection and 2 developed severe chronic rejection requiring retransplantation. These concerns were echoed recently in a larger retrospective study by Walter et al who reported rejection developing in 15 (21%) patients from a pool of 70 recurrent HCV patients after treatment with interferon and ribavirin for an average period of 8 months (range, 1–15 mo). The wide disparity in frequency of rejection between different institutions should not raise unnecessary alarms but may reflect differences in thresholds for performing liver biopsies and their interpretation, immunosuppressive regimens, management of the different grades of rejections, and the variable experiences of programs in recurrent HCV management. Unlike the risks of renal allograft rejection with interferon—the risks of hepatic allograft rejection with interferon appear to be smaller but are not insignificant—careful monitoring of liver function tests while on interferon therapy and a low threshold for performing liver biopsy should be the standard of care.

### Monitoring Disease Progression and Role of Protocol Liver Biopsies

Liver biopsy is considered to be the gold standard for assessing the extent of fibrosis in patients with recur-

### Table 4. Risks and Benefits of Antiviral Therapy for Recurrent HCV

<table>
<thead>
<tr>
<th>Benefits</th>
<th>Risks</th>
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<td>Only medications shown to eradicate recurrent HCV</td>
<td>Frequently ineffective in genotype 1 with SVR often ≤42%</td>
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<tr>
<td>Few randomized studies performed, most data from single-center retrospective studies</td>
<td>Duration of treatment for fibrosing cholestatic HCV unknown</td>
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<tr>
<td>Optimal time for treatment initiation unclear</td>
<td>Dearth of cost-effectiveness studies evaluating pegylated interferon and ribavirin</td>
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<td>Numerous side effects that can be serious and often lead to treatment discontinuation</td>
<td>Expensive</td>
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<td>Progressive fibrosis with decompensation reported despite SVR</td>
<td>Expensive hematologic growth factors often used, data showing improved SVR with their use is poor</td>
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<tr>
<td>Growth factors have their own side effects</td>
<td>In patients with renal failure, interferon dose must be reduced and ribavirin not recommended which decreases SVR further</td>
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<td>Interferon virtually contraindicated in the presence of a renal allograft</td>
<td><strong>Does Interferon Increase the Risk of Hepatic Allograft Rejection?</strong></td>
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Since interferon was first used for treating recurrent HCV more than 10 years ago, there have been concerns the risk of hepatic allograft rejection is increased. Although an early retrospective study on 105 patients treated with interferon did not show any such increase in rejection rates compared with a control group, the interferon-treated patients also received greater baseline immunosuppression. However, Stravitz et al reported that of 23 patients treated with interferon-based therapy for recurrent HCV, 8 (35%) had either acute or chronic rejection and 2 developed severe chronic rejection requiring retransplantation. These concerns were echoed recently in a larger retrospective study by Walter et al who reported rejection developing in 15 (21%) patients (mild n = 5, moderate n = 9, severe n = 1) from a pool of 70 recurrent HCV patients after treatment with interferon and ribavirin for an average period of 8 months (range, 1–15 mo). The wide disparity in frequency of rejection between different institutions should not raise unnecessary alarms but may reflect differences in thresholds for performing liver biopsies and their interpretation, immunosuppressive regimens, management of the different grades of rejections, and the variable experiences of programs in recurrent HCV management. Unlike the risks of renal allograft rejection with interferon—the risks of hepatic allograft rejection with interferon appear to be smaller but are not insignificant—careful monitoring of liver function tests while on interferon therapy and a low threshold for performing liver biopsy should be the standard of care.

### Monitoring Disease Progression and Role of Protocol Liver Biopsies

Liver biopsy is considered to be the gold standard for assessing the extent of fibrosis in patients with recur-
rent HCV. Important limitations including understaging, which can occur in up to 20% of patients, and contraindications such as coagulopathy or thrombocytopenia must be taken into consideration. Transjugular liver biopsies often are performed when obtaining histopathologic diagnosis is essential. Recently, measuring hepatic venous pressure gradients (HVPGs) during transjugular liver biopsies to assess whether it has a predictive function in identifying patients at high risk of hepatic decompensation appeared to show some promise. Samonakis et al\(^6^2\) reported the results of HVPG measurements concomitant with transjugular liver biopsies in 90 consecutive patients with recurrent HCV followed up for a median of 31.5 months. HVPG correlated well with the Ishak fibrosis stage at baseline but when repeated in 49 patients the correlation with fibrosis stage was paradoxically weak (\(r = 0.3, P = .045\)). However, the investigators reported that of the 29 patients with HVPG less than 6 mm Hg at 1 year, none developed hepatic decompensation compared with 31% who developed portal hypertension.

A variety of noninvasive investigations have been studied to evaluate disease progression in recurrent HCV. Benlloch et al\(^6^3\) developed a fibrosis index based on 4 variables (prothrombin time, aspartate aminotransferase level, albumin/total protein ratio, and time since LT) to predict fibrosis. Interestingly, the sensitivity, specificity, positive predictive value, and negative predictive value were similar to the values obtained in pretransplant patients. This model was able to differentiate significant (bridging or cirrhosis) from mild (none or portal) fibrosis, thus possibly obviating the need for a liver biopsy. Piscaglia et al\(^6^4\) used an artificial neural network based on HVPGs during transjugular liver biopsies and HVPG. The investigators reported a sensitivity, specificity, positive predictive value, negative predictive value of 100%, 79.5%, 61%, and 100%, respectively, for predicting significant fibrosis. Recently, transient elastography has shown promise with excellent sensitivity and positive predictive value for mild fibrosis and even greater accuracy for more advanced fibrosis when performed in parallel with liver biopsies and HVPG. Carrion et al\(^6^5\) also reported that no patient with a value less than the liver stiffness cut-off value of 8.5 kPa had bridging fibrosis, cirrhosis, or HVPG greater than 10 mm Hg. It is likely that additional tools such as molecular markers of hepatic fibrosis and detection of stellate cell activation will be used to monitor disease progression based on recent encouraging studies but these investigations, although attractive in concept, need to be reproduced in larger multicenter studies.

Because recurrent HCV can progress silently to cirrhosis in the presence of normal liver function tests, protocol liver biopsies occasionally are performed on an annual basis to assess disease progression before initiating treatment. However, an important question investigators need to ask from the outset is whether this information will alter patient management, particularly given the known limitations of antiviral therapy. Although it may be important to stratify according to stage of fibrosis, protocol biopsies should not be performed unless they answer a specific question such as evaluating the impact of immunosuppression on progression of fibrosis or are performed in the context of a clinical trial. Unlike clinically driven biopsies, which are necessary to evaluate the myriad causes of increased liver function tests in transplant recipients, performing protocol biopsies simply to provide prognostic information appears to be an insufficient indication given both the known limitations of treatment and difficulty in predicting the future of this often unpredictable disease.

### Retransplantation

Retransplantation for recurrent HCV continues to be a vexing, even contentious, management problem. Several studies have reported poor outcomes compared with other liver retransplant recipients, particularly for those transplanted for severe early recurrent HCV occurring within 6–12 months of LT. Other studies have reported comparable outcomes with other transplant recipients provided clear guidelines are followed such as performing retransplantation before patients develop renal failure or severe jaundice (Table 5). However, the policy for retransplantation continues to vary between transplant programs in part owing to subjective differences in perceived results between transplant physicians, surgeons, and the patient–family unit despite widely published data supporting comparable results with non-HCV retransplants if guidelines are followed. A catch-22 situation can develop in which recurrent HCV patients who would appear to benefit most from retransplantation (ie, before onset of severe jaundice or renal failure) may not accrue a MELD score that would justify donor allocation, yet when a donor finally becomes available the patient may be too unwell to survive transplantation.

A recent study was published by McCashland et al\(^6^6\) to address these various controversies. This multicenter retrospective study encompassing the transplant period from 1996 to 2004 compared survival after retransplantation in patients with recurrent HCV (histologically proven) and those transplanted for other indications. Patients were divided into 3 groups: HCV retransplantation, non-HCV retransplantation, and recurrent HCV but

### Table 5. International Liver Transplantation Society Consensus on Retransplantation

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<th>Variables associated with worse outcomes include</th>
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<td>Total bilirubin level &gt;10 mg/dL</td>
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<td>Creatinine level &gt;2 mg/dL</td>
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<td>Age &gt;55 years</td>
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<td>Development of cirrhosis in the first posttransplant year</td>
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<td>Donor age &gt;40 years</td>
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no retransplantation. One- and 3-year survival rates after retransplantation were also similar for HCV retransplantation and non-HCV retransplantation groups (1 y, 69% vs 73%; 3 y, 49% vs 55%). MELD scores were not predictive of survival from retransplantation, probably reflecting the small sample size of patients ($n = 43$), whereas in non-HCV patients with a MELD score of greater than 30, survival was less than 50%. The most common reasons for not listing for retransplantation were recurrent HCV within 6 months (22%), fibrosing cholestatic HCV (19%), and renal dysfunction (9%). The investigators concluded that patients retransplanted for recurrent HCV had similar 1- and 3-year survival rates when compared with patients undergoing retransplantation for other indications although many patients with recurrent HCV were not considered for retransplantation and died from recurrent disease. The role of awarding additional priority MELD points for this group needs to be considered if retransplantation is indicated clinically. Liver transplant centers that refuse to offer retransplantation to patients with recurrent HCV were similar 1- and 3-year survival rates when compared with non-HCV patients with a MELD score of greater than 30, survival was less than 50%. The most common reasons for not listing for retransplantation were recurrent HCV within 6 months (22%), fibrosing cholestatic HCV (19%), and renal dysfunction (9%). The investigators concluded that patients retransplanted for recurrent HCV had similar 1- and 3-year survival rates when compared with patients undergoing retransplantation for other indications although many patients with recurrent HCV were not considered for retransplantation and died from recurrent disease. The role of awarding additional priority MELD points for this group needs to be considered if retransplantation is indicated clinically. Liver transplant centers that refuse to offer retransplantation to patients with recurrent HCV should do so on a case-by-case basis, taking into account recent data suggesting a more optimistic outcome in selected patients.

Conclusions

Hepatitis C is here to stay and will remain the most common indication for LT, despite projections that nonalcoholic fatty liver disease may account for a greater proportion of adult LTs in the future. Treating physicians need to be aware of important issues that affect the natural history of recurrent HCV. The greatest opportunity for HCV eradication is in the pre-LT before hepatic decompensation. Few factors in the posttransplant setting that impact on disease recurrence and outcomes can in reality be adjusted by clinicians. These factors include preservation injury (particularly in the setting of cadaveric donation), immunosuppression, and antiviral therapy. More attention needs to be paid to conducting well-designed studies that study the impact of our interventions on these factors rather than proceeding with large retrospective or single case studies that do not advance our understanding of this disease. A paradigm shift is necessary in our approach to treatment. While waiting for the results of studies of promising new antivirals such as protease inhibitors in pre-LT patients, we need to study these new drugs at the first opportunity in post-LT patients who are at greater risk of rapidly developing cirrhosis.

References


