Drugs 2004; 64 (5): 489-498
0012-6667/04/0005-0489/$34.00/0

Treatment of Hepatitis C in Solid Organ Transplantation

Susan E. Chan,[1,2] *Jonathan M. Schwartz*[1,2] and *Hugo R. Rosen*[1,2]

1 Division of Gastroenterology & Hepatology, Oregon Health & Science University, Portland, Oregon, USA
2 Portland Veterans Affairs Medical Center, Portland, Oregon, USA

Contents

Abstract

Hepatitis C virus (HCV) infection is highly prevalent worldwide, and results in significant morbidity and mortality. HCV frequently infects haemodialysis patients and appears to impact on long-term survival of kidney transplant recipients. Therefore, treatment is recommended for kidney transplant candidates before transplantation and should be avoided following transplantation because of a high risk of allograft rejection. HCV infection does not appear to influence survival in cardiac transplant recipients and cardiac transplant recipients should also not be treated. In general, HCV-infected patients with cirrhosis are not considered as candidates for either kidney or cardiac transplantation given their risk of decompensation. HCV is the most common indication for liver transplantation and re-infection with varying degrees of liver injury is universal. Survival after liver transplantation is reduced among HCV-infected patients when compared with uninfected controls. Therefore, treatment using interferon and ribavirin is advocated; however, such therapy is frequently limited by adverse effects. Thus, improved antiviral treatment modalities are eagerly awaited in the transplant setting.

Hepatitis C virus (HCV) is the major causative agent of chronic hepatitis and has an estimated global prevalence of 3%.[1] Viral persistence is established in the majority of persons acutely infected, and patients are at continued risk of developing HCV-related liver disease and its complications, including cirrhosis and hepatocellular carcinoma. Treatment of immunocompetent patients infected with HCV genotype 1 using pegylated interferons and ribavirin results in sustained virological response rates of between 42% and 46%.[2,3] This review focuses on HCV infection in recipients of solid organ transplantation, including the indications for and efficacy of current antiviral treatment in this setting.

1. Renal Transplantation

The prevalence of HCV in patients with end-stage renal disease is 10-fold that of the general population, ranging from 10% to 36%.[4] However, a recent large study of 2796 haemodialysis patients determined a prevalence of 7%, with only 4% with active viraemia.[5] In less developed countries, with inefficient means of prevention, the infectivity rate approaches 65%.[6] Although the risk of infection by parenteral spread through intravenous drug use and blood transfusions is similar among groups, the primary mode of transmission in patients with chronic renal failure is thought to be nosocomial. The use of infected haemodialysis equipment and inadequate infection control practices are likely to be contributors. Conversely, in some European countries where strict adherence to universal precautions and the use of dedicated equipment has been applied, new cases have been virtually eliminated.[7] Factors associated with higher risk of hepatitis C include the number of years on dialysis, the volume of blood transfused and the type of dialysis.[8] The prevalence of HCV-positivity is >80% for patients on haemodialysis for >20 years. In addition, patients on haemodialysis have a risk 2–3 times greater than those on peritoneal dialysis.

1.1 Diagnosis

Detection of HCV infection in patients with chronic renal failure can be an additional challenge. The serum aminotransferase levels often remain in the normal range; accordingly, it has been suggested that the upper limit of normal for aminotransferases should be lowered in patients with renal failure. Serological tests to detect HCV antibodies can be confounded further by haemodialysis and, therefore, assessment of HCV RNA is often necessary to definitively exclude the diagnosis. Heparin can interfere with the polymerase chain reaction (PCR) assay leading to false-negative results.[9] This effect can be negated by obtaining the specimen before dialysis or on nondialysis days. Moreover, the chronic immunosuppressed state can result in a longer window from the time of infection to seroconversion, resulting in patients who are HCV antibody negative but who have active viraemia.

Several studies have shown a discordance between the histological findings and clinical or laboratory parameters.[10,11] Despite higher RNA titres, HCV-positive patients with end-stage renal disease had a lower prevalence of bridging fibrosis or cirrhosis than viral RNA-positive patients with normal renal function and elevated aminotransferase levels. Transjugular liver biopsy should be considered in patients for whom therapy is being offered because of the risks associated with percutaneous liver biopsy in uraemic patients.

1.2 Natural History

In the general population, infection with HCV causes acute and chronic liver disease with variable rates of progression. The progression of HCV in patients with end-stage renal disease is not well defined, as the higher rate of morbidity and mortality among this group of patients has precluded long-term follow up. The immunosuppressed state of these patients both before and after renal transplantation may be associated with increased rates of viral replication. An increased incidence of liver cancer has been suggested in pretransplant, dialysis-dependent patients.[12] Primary prevention aimed at reducing the rate of new cases as well as secondary prevention with early detection and treatment prior to transplantation are important goals to reduce the impact of HCV infection effectively in this patient population.

The impact of HCV on graft function and patient survival after transplant remains a question of debate. The initial data suggested no significant difference in patient or graft survival at 5 years between

Table I. Studies of interferon (IFN)-α monotherapy for hepatitis C virus infection in patients undergoing haemodialysis

Study[a]	Patients (n)	Duration of therapy (mo)	IFNα dosage (MU TIW)	Sustained virological response (%)	Follow up (mo)
Espinosa et al.[19]	13	12	3	6/13 (46.2)	60
Huraib et al.[20]	15	12	3	4/15 (26.7)	12
Hanrotel et al.[21]	12	12	3	4/12 (33.3)	12
Degos et al.[22]	37	12	1.5–3	7/37 (18.9)	6
Campistol et al.[23]	19	6	3	8/19 (42.1)	21
Benci et al.[24]	10	12	1[b]	2/10 (20)	6
Chan et al.[25]	11	6	3	3/11 (27.3)	24
Izopet et al.[26]	23	6–12	3	12 (52.2)	19
Fernandez et al.[27]	14	6	1.5–3	2/14 (14.3)	12
Pol et al.[28]	19	6	3	3/19 (15/8)	18
Raptopoulou-Gigi et al.[29]	19	6	1–3	12/19 (63.2)	14
Koenig et al.[30]	37	4	5	11/37 (29.7)	5

a Order by year of publication, most recent first.

b Treatment with leucocyte IFNα.

TIW = three times weekly.

HCV antibody-positive and HCV antibody-negative transplant recipients. However, in more recent studies both patient and graft survival have been negatively impacted.[13,14] In one study, potential confounding variables (age, immunosuppression, date of transplant) were controlled for in a case-control format, and HCV infection was found to be independently associated with poorer outcomes.[15]

1.3 Indications for Treatment

Treatment of hepatitis C in the pretransplant patient may have a positive impact on the effect the long-term complications of hepatitis C have on patient and graft survival after transplantation. Interferon exerts its effect via immunomodulatory activity and suppression of cell prolifreration and viral replication. Decreased clearance of the drug in patients undergoing haemodialysis is suggested by higher mean maximum serum concentrations and a longer half-life compared with in patients with normal renal function.[16] This is likely to contribute to the poor tolerance of the therapy seen in patients undergoing haemodialysis, which often requires discontinuation of the medication or a reduction in dosage.[17] In patients with renal impairment, interferon (IFN)-α monotherapy has been shown to be achieve a sustained virological response in those undergoing haemodialysis. The studies published to date on haemodialysis patients treated with antiviral therapy are outlined in table I; overall, the responses to antiviral therapy are similar to those seen in patients without renal disease. Currently, the sustainability of these responses, that is the proportion of virologic responders who remain HCV RNA-negative after renal transplantation, remains undefined, although in a recent study a maintained response 41 ± 28 months after transplant was achieved in eight patients.[18]

In addition, the treatment of chronic hepatitis C requires consideration of the severity of liver disease on biopsy, the general medical condition of the patient and candidacy for transplantation. A practical algorithm, as outlined by Morales and Campistol[31] directs therapy based on liver histology. Using this model, all patients who are HCV-RNA positive receive a liver biopsy. Those with normal histology are not treated, whereas those with evidence of chronic hepatitis receive IFNα monotherapy. Lastly, patients with clinical or histological evidence of cirrhosis should be considered for simultaneous kidney and liver transplantation.

1.4 Treatment Modalities

The aims of therapy are 2-fold, viral eradication and improvement of liver histology. Generally, treatment is aimed at pretransplant, chronic dialysis patients. In the general population, treatment with IFNα monotherapy achieves a 15–25% sustained

response.[32] IFN monotherapy in haemodialysis patients has resulted in a sustained virological response in 15.8–64%.[33]

Combination therapy with IFNα and ribavirin has become the standard of care in the general population given the superior efficacy over IFNα monotherapy.

In patients with renal dysfunction, ribavirin clearance is markedly diminished. Furthermore, no dose administration guidelines have been established for its use in this population of patients, although it has been suggested that a dose of 200 mg/day maintains serum trough concentrations equal to a standard dose in patients with normal renal function (approximately 1000–1200 mg/day).[34] Although a potential for improved efficacy has been demonstrated, there is a marked increase in adverse events, most commonly persistent, severe anaemia, which resolves with the discontinuation of therapy.[34] For these reasons, as well as the limited experience with ribavirin therapy in combination with IFNα, this regimen is recommended only for patients who do not respond to or who relapse after discontinuation of IFNα monotherapy.

The use of pegylated IFNs in immune competent patients has increased significantly, suggesting a possible role in the treatment of haemodialysis patients. A recently published study evaluating the pharmacokinetics of pegylated IFNα-2b in patients with varying degrees of renal dysfunction has demonstrated longer half-life and greater maximum serum concentrations in patients whose creatinine clearance is <30 mL/min compared with those with normal renal function.[35] Studies evaluating the efficacy of the pegylated IFNs in haemodialysis patients are underway and the use of these agents cannot be advocated until these data are available.

Following renal transplantation, the safety and efficacy of IFNα therapy is not proven. In fact, renal transplant recipients are at risk for allograft rejection and renal dysfunction during IFNα treatment, even in patients with long-term stable allograft function. Several small studies have demonstrated moderate biochemical efficacy with minimal virological response, associated with renal impairment.[36-38] The largest study of this kind included 16 kidney transplant recipients with chronic hepatitis C.[38] Although biochemical normalisation was achieved in 15 patients, no patient had sustained virological response. Six of 16 patients experienced renal failure during therapy. Currently, IFNα therapy is only indicated after transplant for fibrosing cholestatic hepatitis.[31] The poor tolerability of IFNα and risk of allograft rejection emphasise the importance of pre-emptive antiviral therapy in the pretransplant period. Until less toxic therapies are available for hepatitis C, attempted slowing of the progression of viral replication can be made through attempted reduction of the immunosuppressive medications; however, the subgroup of patients most likely to benefit from this approach has not yet been defined. Management issues are further highlighted in two recently published reviews.[39,40]

2. Cardiac Transplantation

As with other organs, the number of potential recipients of cardiac transplants vastly exceeds the number of available donor organs. By International Classification of Diseases (ICD-9)[41] diagnosis, there are 40 000 potential recipients of cardiac transplantation in the US between infancy and 65 years of age,[42] yet only 2500 donor organs are available. Given the high prevalence of HCV in the general population, coupled with the donor shortage, issues regarding the diagnosis, outcome and management of HCV infection in this population are vital. This section reviews the data regarding outcomes of patients with pre-existing chronic HCV infection undergoing cardiac transplantation, the impact of *de novo* HCV infection following transplantation, and discusses the diagnostic and therapeutic approach to such individuals.

2.1 Transmission of Hepatitis C Virus (HCV) Via Cardiac Transplantation

Solid organ transplantation is a well established risk factor for HCV transmission. Transplantation of HCV antibody positive donor organs into uninfected recipients almost uniformly results in chronic HCV infection in the immunocompromised host.[43-45] The long-term consequences of HCV transmission in this cohort of patients is not presently known; however, in the short term (up to 42 months), overall recipient survival does not appear to be affected significantly.[44]

2.2 Diagnosis of HCV Infection Following Cardiac Transplantation

Up to one-third of heart transplant recipients with HCV infection do not develop detectable antibody responses as a consequence of their immunosuppressed state.[43,44,46,47] In addition, as observed by Lunel, et al.,[48] patients with *de novo* HCV infection following cardiac transplantation have a significant delay between aminotranferase elevation or HCV RNA detection and anti-HCV detection. Therefore, if HCV infection is suspected on the basis of elevated serum aminotransferases or cholestasis, the use of PCR technology to detect HCV RNA is required.

2.3 Outcomes of Patients with Pre-Existing HCV Infection

Studies addressing the outcome of cardiac transplant recipients with pre-existing HCV infection have been limited by the small number of patients and relatively short duration of follow up.[47,49,50] Nevertheless, HCV infection does not appear to result in increased mortality among cardiac transplant recipients. In a study by Lake et al.,[50] increased liver-related mortality was observed in HCV-infected recipients when compared with uninfected patients; however, there was no difference in all-cause mortality between these two cohorts.

There appears to be agreement in the transplant community that patients with advanced HCV-related fibrosis or cirrhosis are not ideal candidates for cardiac transplantation given that such individuals might have a reduced life expectancy because of their underlying liver disease.[42]

2.4 Natural History of Patients with *de novo* HCV Infection After Cardiac Transplantation

In general, patients with *de novo* HCV infection are likely to have an indolent course despite their immunosuppressed state. A relatively large, prospective study[48] did not observe significant short-term differences in the rate of fibrosis progression when HCV-infected cardiac transplant recipients were compared with immunocompetent patients with HCV infection. In addition, *de novo* HCV infection does not appear to reduce short-term and intermediate-term survival after cardiac transplantation.[46,48] Patients with *de novo* HCV infection after cardiac transplantation are at risk of developing a form of severe cholestatic HCV infection with a subsequent increase in mortality.[46,47] In addition, the use of mycophenolate mofetil was associated with increased mortality in HCV-infected transplant recipients in one study.[46]

2.5 Use of HCV-Positive Donor Organs in HCV-Positive Recipients and HCV-Negative Recipients

Although no standardised policy exists, a survey of cardiac transplant centres noted that approximately two-thirds of US centres offer cardiac transplantation to HCV-infected recipients.[51] In addition, in order to increase the number of organs available for transplantation, many centres transplant allografts from HCV-infected donors to HCV-infected recipients. Moreover, given the risk of progressive liver injury related to HCV infection post-transplant there appears to be agreement that the use of HCV-infected donors for uninfected recipients should be limited to those recipients in urgent need of cardiac transplantation.

2.6 Treatment of HCV Disease in the Setting of Cardiac Transplantation

No data are available regarding IFN-based antiviral therapy for HCV-infected cardiac transplant candidates or recipients. The adverse effect profile of the combination of IFNα and ribavirin therapy[52] (which currently achieves the highest rates of viral eradication),[53,54] would limit the ability of patients with severe cardiac dysfunction to tolerate such therapy. At this point, we cannot recommend IFN-based therapy in this group of patients unless in the setting of a highly monitored clinical trial. In addition, as in renal allograft recipients, we cannot endorse the use of IFN-based antiviral therapy following cardiac transplantation. Such therapy is likely to place the recipient at risk of allograft rejection. Given these limitations, the development of well tolerated and effective non-IFN-based antiviral therapies is eagerly awaited.

3. HCV Infection and Lung Transplantation

Little data exist regarding outcomes after lung transplantation in recipients with pre-existing or *de novo* HCV infection. A recent survey of lung transplant centres in the US[55] noted that 72% of centres performed transplants in HCV-infected patients. Most centres screen potential transplant candidates for HCV and use liver biopsy data to determine candidacy. In this survey, approximately one-half of the programmes used HCV-infected donor organs, of which most were designated for recipients with pre-existing HCV.

Data regarding the safety and efficacy of IFN-based therapy for HCV infection in lung transplant candidates or recipients are not available. Patients with advanced lung disease would probably not be good candidates for pretransplant antiviral therapy and the risk of allograft rejection would probably outweigh any benefit of antiviral therapy for HCV in lung transplant recipients.

4. Natural History of HCV Disease Following Liver Transplantation

HCV-related liver disease is the leading indication for orthotopic liver transplantation (OLT) worldwide. HCV reinfection after OLT universally occurs in patients with pretransplantation viraemia and 50–80% of these patients develop graft hepatitis.[56] Although most studies demonstrate that graft and patient survival for the first decade following OLT appears to be unaffected by the HCV serostatus of the recipient, these analyses were likely to have been underpowered to detect small differences. Accordingly, a recent analysis of the United Network for Organ Sharing (UNOS) database[57] demonstrated significantly diminished survival at 5 years following primary OLT in HCV-positive patients (65.6% vs 56.7% for HCV-negative vs HCV-positive recipients, respectively).

The natural history of recurrent HCV infection was described by the King's College group by comparing 1- and 5-year protocol biopsies from OLT recipients with and without HCV infection.[58] Almost 90% of the HCV-infected patients (n = 149) had chronic hepatitis by 5 years compared with approximately 20% of the HCV-negative group (n = 623, in whom allograft hepatitis was predominantly related to hepatitis B virus [HBV] infection). Of concern, 20% of the HCV-infected patients had evidence of allograft cirrhosis at the 5-year protocol biopsy; therefore, the natural history of HCV infection appears truncated in OLT recipients compared with immunocompetent individuals. Although studies with longer follow-up are required to determine the proportion of patients who will ultimately develop allograft cirrhosis and graft failure related to HCV recurrence, it appears that fewer than 10% of patients with mild hepatitis at 1-year progress to allograft cirrhosis at 5 years. In contrast, two-thirds of patients with at least moderate activity at 1-year progressed to cirrhosis by 5 years in the King's College series. A recent study by Berenguer et al.[59] evaluated the natural history of post-OLT HCV infection by assessing rate of fibrosis progression. The median fibrosis progression per year was significantly higher than in the immunocompetent setting, with the median duration to cirrhosis about 10 years. Variables independently associated with a higher post-transplantation fibrosis progression included a transplant in the past 5 years, race other than Caucasian, any number of methylprednisolone boluses and a higher viral load at transplantation.

What is the natural history of patients who develop allograft cirrhosis? An additional study by the Valencia group[60] evaluated the natural history of HCV-related graft cirrhosis to define the rate of clinical decompensation and mortality. Thirty-nine patients with clinically compensated allograft cirrhosis were studied; 18 (46%) developed at least one episode of decompensation with a mean of approximately 8 months post development of allograft cirrhosis. Compared with the data generated by Fattovich et al.,[61] this rate was considerably higher than in nontransplanted patients with cirrhosis. Moreover, patient survival rates following development of allograft decompensation were abysmal: 93%, 61% and 41% at 1, 6 and 12 months, respectively.[60] Variables associated with decompensation and death included a short interval between OLT and development of allograft cirrhosis, and a high Child-Pugh score (>A). The study concluded that if re-transplantation is considered, it should be performed promptly once decompensation develops.

4.1 When to Treat?

A study by Gretch et al.[62] demonstrated that serum HCV RNA levels in the first 2 weeks following OLT were significantly higher among patients who subsequently developed chronic active hepatitis within their allografts versus those patients who did not. A longitudinal analysis by Gane et al.[63] found that the onset of acute allograft hepatitis was associated with peak circulating levels of HCV RNA, which in the majority of patients decreased over time. Moreover, an analysis of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) liver transplant database showed the predictive value of pretransplant viral levels: patients with circulating HCV RNA levels $>1 \times 10^6$ eq/mL just before OLT had significantly diminished graft and patient survival,[64] suggesting that the size of the viral *innoculum* is crucial and providing a rationale for pre-emptive therapy in a subset of patients. On the basis of these data, some[65] have suggested that antiviral treatment should be initiated in patients with high viral loads before histological recurrence, either before transplantation or within the first few weeks after transplantation.

Results from several trials using pre-emptive antiviral therapy after transplant but before histological recurrence have been unimpressive.[66-68] However, 15 patients treated before liver transplantation in a recent pilot study demonstrated multiple, severe adverse effects and reduction of viral load in only a minority of patients.[69] On the other hand, data from the University of Colorado[70] suggest that a low accelerating-dose antiviral regimen (starting at IFNα-2b 1.5MU three times weekly for 2 weeks and then increased to a standard 3MU three times weekly; ribavirin starting at 600 mg/day and increased every 2 weeks to a maximum total dosage of 1200 mg/day) achieved sustained virologic clearance in eight of 64 (12.5%) patients awaiting liver transplantation. More importantly, none of the eight patients who were HCV RNA-negative at the time of transplant have a recurrence after liver transplantation. These preliminary data are highly encouraging and suggest that viral eradication is possible in a subset of patients with endstage liver disease and this translates into improved outcome after transplantation.

Most of the published work has focused on treatment of established recurrence and results with combination IFNα plus ribavirin therapy, while encouraging when compared with monotherapy, have underscored the severe adverse effects in a significant proportion of patients. This problem is particularly salient when one considers that most of the published trials have excluded patients with severe recurrence, that is, those patients for whom therapy is most likely to be cost effective.[71] Common adverse effects of IFNα include a flu-like syndrome, depression and dose-related myelosuppression. Up to 20% of liver transplant recipients treated with IFNα require cessation of the drug because of cytopenias.[72] The most frequent adverse effect of ribavirin is haemolysis, and this is potentiated in liver transplant patients because of reduced renal clearance as a result of calcineurin inhibitor-induced nephrotoxicity and HCV-related glomerulonephritis.[72] A recent study demonstrated the utility of measuring creatinine clearance as a predictor of the need for ribavirin dosage-adjustments in liver transplant patients.[73] However, administration of granulocyte colony-stimulating factor and erythropoietin may allow reinstitution of full dose antiviral therapy.[74] In patients treated with combination IFNα plus ribavirin, intention-to-treat end of treatment response rates have ranged from 27% to 53% and sustained response rates have ranged from 17% to 27%.[72,75,76] Unfortunately, on the average, one-third of patients are unable to complete treatment because of drug-related serious adverse events.[72] Emerging data on the use of pegylated IFNα with ribavirin have shown very encouraging preliminary results in liver transplant patients.[77]

4.2 How Long to Treat?

Although most clinicians treat recurrent HCV according to guidelines for immunocompetent patients, controlled trials are required to define the optimal duration of therapy after liver transplantation. In this regard, a recent study from Italy[78] showed an approximately 20% sustained virologic response rate irrespective of whether the patients received a 6- or 12-month course of combination therapy. In contrast, the subset of patients who develop severe cholestatic recurrence may require an

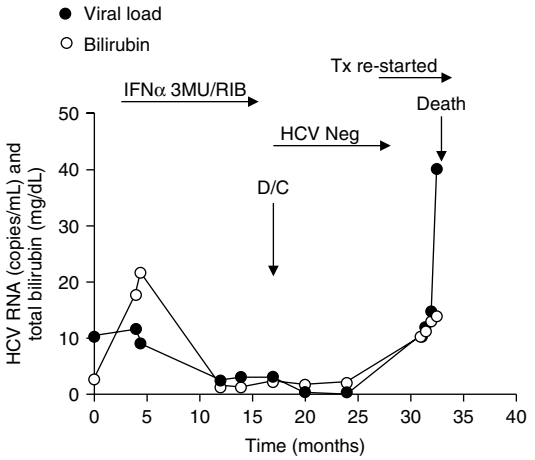

Fig. 1. A patient with severe cholestatic hepatitis C virus (HCV) recurrence who cleared HCV RNA with standard interferon-α (IFNα)-2b plus ribavirin (RIB) treatment; after cessation of antiviral therapy (D/C), he developed relapse of cholestatic syndrome and died (reproduced from Gopal and Rosen,[79] with permission from the American Association for the Study of Liver Diseases). **Neg** = negative; **Tx** = treatment.

indefinite duration of treatment as indicated by our centre's own experience[79] (figure 1).

5. Concluding Perspectives

The evolution of our understanding of the natural history and management of HCV infection in the solid organ recipient has been rapid in the last decade. However, our knowledge on the factors identifying patients at increased risk of progression of underlying liver disease in kidney, heart or lung recipients, and the severity of recurrence in liver transplant patients, is incomplete. It is hoped that effective and 'safe' prophylactic and therapeutic regimens will be developed that alter the natural history of HCV infection, and diminish the rate of patient and graft loss.

Acknowledgements

Supported by Veterans Affairs and National Institutes of Health Funding. The authors have no conflicts of interest that are directly relevant to the content of this manuscript.

References

1. Alter MJ, Kruszon-Moran D, Nainan OV, et al. The prevalence of hepatitis C virus infection in the United States, 1988 through 1994. N Engl J Med 1999; 341: 556-62
2. Manns MP, McHutchinson JG, Gordon SC, et al. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomized trial. Lancet 2001; 358: 958-65
3. Fried MW, Shiffman ML, Reddy KR, et al. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. N Engl J Med 2002; 347: 975-82
4. Recommendations for preventing transmission of infections among chronic hemodialysis patients. MMWR Recomm Rep 2001; 50: 1-43
5. Hinrichsen H, Leimenstoll G, Stegen G, et al. Prevalence and risk factors of hepatitis C virus infection in haemodialysis patients: a multicentre study in 2796 patients. Gut 2002; 51: 429-33
6. Rosen HR, Friedman L, Martin P. Hepatitis C and the renal transplant patient. Semin Dial 1996; 9: 39-47
7. Jadoul M, Cornu C, van Ypersele de Stirhou C. Universal precautions prevent hepatitis C virus transmission: a 54 month follow-up of the Belgian Multicenter Study. The Universitaires Cliniques St-Luc (UCL) Collaborative Group. Kidney Int 1998; 53: 1022-5
8. Genesca J, Vila J, Cordoba J, et al. Hepatitis C virus infection in renal transplant recipients: epidemiology, clinical impact, serological confirmation and viral replication. J Hepatol 1995; 22: 272-7
9. Willems M, Moshage H, Nevens F, et al. Plasma collected from heparinized blood is not suitable for HCV-RNA detection by conventional RT-PCR assay. J Virol Methods 1993; 42: 127-30
10. Sterling RK, Sanyal AJ, Luketic VA, et al. Chronic hepatitis C infection in patients with end stage renal disease: characterization of liver histology and viral load in patients awaiting renal transplantation. Am J Gastroenterol 1999; 94: 3576-82
11. Cotler SJ, Diaz G, Gundlapalli S, et al. Characteristics of hepatitis C in renal transplant candidates. J Clin Gastroenterol 2002; 35: 191-5
12. Maisonneuve P, Agodoa L, Gellert R, et al. Cancer in patients on dialysis for end-stage renal disease: an international collaborative study. Lancet 1999; 354: 93-9
13. Kokado Y, Takahara S, Ichimaru N, et al. Clinical outcome of HCV infection after renal transplantation. Transplant Proc 2000; 32: 1940-3
14. Mas V, Alvarellos T, Chiurchiu C, et al. Hepatitis C virus infection after renal transplantation: viral load and outcome. Transplant Proc 2001; 33: 1791-3
15. Mathurin P, Mouquet C, Poynard T, et al. Impact of hepatitis B and C virus on kidney transplantation outcome. Hepatology 1999; 29: 257-63
16. Rostaing L, Chatelut E, Payen JL, et al. Pharmacokinetics of alpha IFN-2B in chronic hepatitis C virus patients undergoing chronic hemodialysis or with normal renal function: clinical implications. J Am Soc Nephrol 1998; 9: 2344-8
17. Degos F, Pol S, Chaix ML, et al. The tolerance and efficacy of interferon-alpha in haemodialysis patients with HCV infection: a multicentre, prospective study. Nephrol Dial Transplant 2001; 16: 1017-23
18. Casanovas-Taltavull T, Baliellas C, Benasco C, et al. Efficacy of interferon for chronic hepatitis C virus-related hepatitis in kidney transplant candidates on hemodialysis: results after transplantation. Am J Gastroenterol 2001; 96: 1170-7
19. Espinosa M, Rodriguez M, Martin-Malo A, et al. Interferon therapy in hemodialysis patients with chronic hepatitis C virus infection induces a high rate of long-term sustained virological and biochemical response. Clin Nephrol 2001; 55: 220-6
20. Huraib S, Iqbal A, Tanimu D, et al. Sustained virological and histological response with pretransplant interferon therapy in renal transplant patients with chronic viral hepatitis C. Am J Nephrol 2001; 21: 435-40

21. Hanrotel C, Toupance O, Lavaud S, et al. Virological and histological responses to one year alpha-interferon-2a in hemodialyzed patients with chronic hepatitis C. Nephron 2001; 88: 120-6
22. Degos F, Pol S, Chaix ML, et al. The tolerance and efficacy of interferon-alpha in haemodialysis patients with HCV infection: a multicentre, prospective study. Nephrol Dial Transplant 2001; 16: 1017-23
23. Campistol JM, Esforzado N, Martinez J, et al. Efficacy and tolerance of interferon-alpha (2b) in the treatment of chronic hepatitis C virus infection in haemodialysis patients. Pre- and post-renal transplantation assessment. Nephrol Dial Transplant 1999; 14: 2704-9
24. Benci A, Caremani M, Menchetti D, et al. Low-dose leukocyte interferon-alpha therapy in dialysed patients with chronic hepatitis C. Curr Med Res Opin 1998; 14: 141-4
25. Chan TM, Wu PC, Lau JY, et al. Interferon treatment for hepatitis C virus infection in patients on haemodialysis. Nephrol Dial Transplant 1997; 12: 1414-9
26. Izopet J, Rostaing L, Moussion F, et al. High rate of hepatitis C virus clearance in hemodialysis patients after interferon-alpha therapy. J Infect Dis 1997; 176: 1614-7
27. Fernandez JL, Rendo P, del Pino N, et al. A double-blind controlled trial of recombinant interferon-alpha 2b in haemodialysis patients with chronic hepatitis C virus infection and abnormal aminotransferase levels: Nephrologists' Group for the Study of HCV infection. J Viral Hepat 1997; 4: 113-9
28. Pol S, Thiers V, Carnot F, et al. Efficacy and tolerance of alpha-2b interferon therapy on HCV infection of hemodialyzed patients. Kidney Int 1995; 47: 1412-8
29. Raptopoulou-Gigi M, Spaia S, Garifallos A, et al. Interferon-alpha 2b treatment of chronic hepatitis C in haemodialysis patients. Nephrol Dial Transplant 1995; 10: 1834-7
30. Koenig P, Vogel W, Umlauft F, et al. Interferon treatment for chronic hepatitis C virus infection in uremic patients. Kidney Int 1994; 45: 1507-9
31. Morales JM, Campistol JM. Transplantation in the patient with hepatitis C. J Am Soc Nephrol 2000; 11: 1343-53
32. Hoofnagle JH, di Bisceglie AM. The treatment of chronic viral hepatitis. N Engl J Med 1997; 336: 347-56
33. Fabrizi F, Poordad FF, Martin P. Hepatitis C infection and the patient with end-stage renal disease. Hepatology 2002; 36: 3-10
34. Tan AC, Brouwer JT, Glue P, et al. Safety of interferon and ribavirin therapy in haemodialysis patients with chronic hepatitis C: results of a pilot study. Nephrol Dial Transplant 2001; 16: 193-5
35. Gupta SK, Pittenger AL, Swan SK, et al. Single-dose pharmacokinetics and safety of pegylated interferon-alpha 2b in patients with chronic renal dysfunction. J Clin Pharmacol 2002; 42: 1109-15
36. Takahara S, Kakimoto K, Kokado Y, et al. Interferon alpha therapy for chronic active hepatitis type C after renal transplantation and allograft rejection. Int Urol Nephrol 1995; 27: 479-85
37. Durlik M, Gaciong Z, Rowinska D, et al. Long-term results of treatment of chronic hepatitis B, C and D with interferon-alpha in renal allograft recipients. Transpl Int 1998; 11 Suppl. 1: S135-9
38. Rostaing L, Izopet J, Baron E, et al. Preliminary results of treatment of chronic hepatitis C with recombinant interferon alpha in renal transplant patients. Nephrol Dial Transplant 1995; 10 Suppl. 6: 93-6
39. Fabrizi F, Poordad FF, Martin P. Hepatitis C infection and the patient with end-stage renal disease. Hepatology 2002; 36: 3-10
40. Gane E, Pilmore H. Management of chronic viral hepatitis before and after renal transplantation. Transplantation 2002; 74: 427-37
41. International Classification of Diseases. 9th rev. Geneva: World Health Organization, 1977
42. Steinman TI, Becker BN, Frost AE, et al. Guidelines for the referral and management of patients eligible for solid organ transplantation. Transplantation 2001; 71: 1189-204
43. Pereira BJ, Milford EL, Kirkman RL, et al. Prevalence of hepatitis C virus RNA in organ donors positive for hepatitis C antibody and in the recipients of their organs. N Engl J Med 1992; 327: 910-5
44. Pereira BJ, Wright TL, Schmid CH, et al. A controlled study of hepatitis C transmission by organ transplantation: the New England Organ Bank Hepatitis C Study Group. Lancet 1995; 345: 484-7
45. Pfau PR, Rho R, DeNofrio D, et al. Hepatitis C transmission and infection by orthotopic heart transplantation. J Heart Lung Transplant 2000; 19: 350-4
46. Ong JP, Barnes DS, Younossi ZM, et al. Outcome of de novo hepatitis C virus infection in heart transplant recipients. Hepatology 1999; 30: 1293-8
47. Zein NN, McGreger CG, Wendt NK, et al. Prevalence and outcome of hepatitis C infection among heart transplant recipients. J Heart Lung Transplant 1995; 14: 865-9
48. Lunel F, Cadranel JF, Rosenheim M, et al. Hepatitis virus infections in heart transplant recipients: epidemiology, natural history, characteristics, and impact on survival. Gastroenterology 2000; 119: 1064-74
49. Castella M, Tenderich G, Koerner MM, et al. Outcome of heart transplantation in patients previously infected with hepatitis C virus. J Heart Lung Transplant 2001; 20: 595-8
50. Lake KD, Smith CI, Milfred-La Forest SK, et al. Outcomes of hepatitis C positive (HCV+) heart transplant recipients. Transplant Proc 1997; 29: 581-2
51. Lake KD, Smith CI, LaForest SK, et al. Policies regarding the transplantation of hepatitis C-positive candidates and donor organs. J Heart Lung Transplant 1997; 16: 917-21
52. Fried MW. Side effects of therapy of hepatitis C and their management. Hepatology 2002; 36: S237-44
53. Fried MW, Shiffman ML, Reddy KR, et al. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. N Engl J Med 2002; 347: 975-82
54. Manns MP, McHutchison JG, Gordon SC, et al. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. Lancet 2001; 358: 958-65
55. Cotler SJ, Jensen DM, Kesten S. Hepatitis C virus infection and lung transplantation: a survey of practices. J Heart Lung Transplant 1999; 18: 456-9
56. Fukumoto T, Berg T, Ku Y, et al. 1996 Viral Dynamics of hepatitis C early after orthotopic liver transplantation: evidence for rapid turnover of serum virions. Hepatology 1996; 24: 1351-4
57. Forman LM, Lucey MR. Orthotopic liver transplantation for hepatitis C: analysis of allograft survival using the UNOS database [abstract no. 82]. Am J Transplant 2001; 1 Suppl. 1: 156
58. Gane EJ, Portmann BC, Naoumouv NV, et al. Long-term outcome of hepatitis C infection after liver transplantation. N Engl J Med 1996; 334: 821-7
59. Berenguer M, Ferell L, Watson J, et al. HCV-related fibrosis progression following liver transplantation: increase in recent years. J Hepatol 2000; 32: 673-84
60. Berenguer M, Prieto M, Rayon JM, et al. Natural history of clinically compensated hepatitis C virus-related graft cirrhosis after liver transplantation. Hepatology 2000; 32 (4 Pt 1): 852-8

61. Fattovich G, Giustina G, Degos F, et al. Morbidity and mortality in compensated cirrhosis type C: a retrospective follow-up study of 384 patients. Gastroenterology 1997; 112: 463-72
62. Gretch DR, Bacchi CE, Corey L, et al. Persistent hepatitis C virus infection after liver transplantation: clinical and virological features. Hepatology 1995; 22: 1-9
63. Gane EJ, Naoumov NV, Qian K-P, et al. A longitudinal analysis of hepatitis C virus replication following liver transplantation. Gastroenterology 1996; 110: 167-77
64. Charlton M, Seaberg E, Wiesner R, et al. Predictors of patient and graft survival following liver transplantation for hepatitis C. Hepatology 1998; 28: 823-30
65. Charlton M. Pre-emptive treatment of recurrent hepatitis C infection. Liver Transpl 2002; 8: S50-4
66. Sheiner PA, Boros P, Klion FM, et al. The efficacy of prophylactic interferon alfa-2b in preventing recurrent hepatitis C after liver transplantation. Hepatology 1998; 28: 831-8
67. Singh N, Gayowski T, Wannstedt CF, et al. Interferon-alpha for prophylaxis of recurrent viral hepatitis C in liver transplant recipients: a prospective, randomized, controlled trial. Transplantation 1998; 65: 82-6
68. Mazzaferro V, Tagger A, Schiavo M, et al. Prevalence of recurrent hepatitis C after liver transplantation with early interferon and ribavirin treatment. Transplant Proc 2001; 33: 1355-7
69. Crippin JS, McCashland T, Terrault N, et al. A pilot study of the tolerability and efficacy of antiviral therapy in hepatitis C virus-infected patients awaiting liver transplantation. Liver Transpl 2002; 8: 350-5
70. Everson GT, Trotter J, Kugelmas M. Long-term outcome of patients with chronic hepatitis C and decompensated liver disease treated with the LADR protocol (low-accelerating-dose regimen) [abstract]. Hepatology 2002; 36 (2): 297A
71. Saab S, Ly D, Han SB, et al. Is it cost-effective to treat recurrent hepatitis C infection in orthotopic liver transplantation patients? Liver Transpl 2002; 8: 449-57
72. Gane E. Treatment of recurrent hepatitis C. Liver Transpl 2002; 8: S28-37
73. Jain AB, Eghtesad B, Venkataramanan R, et al. Ribavirin dose modification based on renal function is necessary to reduce hemolysis in liver transplant patients with hepatitis C virus infection. Liver Transpl 2002; 8: 1007-13
74. Gopal D, Rabkin JM, Berk B, et al. Treatment of progressive HCV recurrence following liver transplatation with combination interferon and ribavirin therapy. Liver Transpl 2001; 7: 181-90
75. de Vera ME, Smallwood GA, Rosado K, et al. Interferon-a and ribavirin for the treatment of recurrent hepatitis C after liver transplantation. Transplantation 2001; 71: 678-86
76. Narayanan Menon KV, Poterucha JJ, El-Amin OM, et al. Treatment of posttransplantation recurrence of hepatitis C with interferon and ribavirin: lessons on tolerability and efficacy. Liver Transpl 2002; 8: 623-9
77. Riely C, Ferenci P, Peck-Radosavljevic M, et al. Pegylated (40 kDa) interferon alfa-2A (pegysus) in post-liver transplant recipients with established recurrent hepatitis C: a preliminary report [abstract 89]. Am J Transplantation 2001; 1 Suppl. 1: 158
78. Lavezzo B, Franchello AA, Smedile A, et al. Treatment of recurrent hepatitis C in liver transplants: efficacy of a six versus twelve month course of interferon alfa 2b with ribavirin. J Hepatol 2002; 37: 247-52
79. Gopal DV, Rosen HR. Duration of antiviral therapy for cholestatic HCV recurrence may need to be indefinite. Liver Transpl 2003; 9: 348-53

Correspondence and offprints: Dr *Hugo R. Rosen*, Division of Gastroenterology & Hepatology, Oregon Health & Science University & Portland Veterans Affairs Medical Center, 3710 SW US Veterans Hospital Rd, PO Box 1034, P3-GI, Portland, OR 97201, USA.
E-mail: hugo.rosen@med.va.gov