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Kidney Transplantation from Donors with a Positive Serology for Hepatitis C: The Facts and the Challenges

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Abstract

The use of kidneys from donors with a positive serology for hepatitis C virus into recipients with anti-HCV-positive antibodies seems to be a safe approach in the long term. Results provided by center-based experiences show a favorable outcome of HCV-positive recipients in terms of graft survival, patient survival, and HCV-related liver disease with kidneys transplanted from HCV-positive donors. Registry studies have raised doubts on the safety of this approach, but do not represent a standardized policy. The safety of this policy can be improved by limiting the transplantation of these kidneys to patients with a positive HCV RNA before transplantation and, ideally, by matching donors and recipients according to the HCV genotype. Kidneys from HCV-positive donors are being lost today because of remaining doubts that seem to be reasonably overcome nowadays and by the lack of appropriate recipients. Organizational measures, such as devising preemptive transplantation for HCV RNA-positive recipients accepting to be transplanted with kidneys from HCV-positive donors, and international cooperation seem essential to avoid the loss of these organs at a moment of dramatic organ shortage. **(Trends in Transplant. 2010;4:129-37)**

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Key words

Kidney transplantation. Hepatitis C. Interferon. Liver disease. Donors.

Introduction

Organ transplantation has become a consolidated therapy which saves the lives or improves the qualities of life of about 100,000 patients worldwide every year[1]. However, one of the main obstacles that preclude the full development of transplantation is the shortage of organs to satisfy the need. At the end of 2009 there were 63,000 patients in the waiting list for an organ in the European Union, while only about 28,000 transplant procedures were performed during that entire year[2]. The UNOS registry shows a rather similar dramatic situation for the USA. In November 2010 more than 100,000 patients were registered in the waiting list, but the number of transplant procedures performed annually in that country is about 28,000[3]. As a consequence of shortage, patients with low survival expectancies

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might not be included in the lists and many will deteriorate or die while waiting to be transplanted. Added to the unequal distribution of wealth in the world, organ shortage is the root case for unacceptable practices such as organ trafficking and transplant tourism[4].

Different strategies have been devised to increase organ availability, including the use of organs from expanded criteria donors[5] and from non standard risk donors. A hazard of a decreased graft survival is assumed in the first case and a hazard of donor-derived diseases in the second. Since hepatitis C virus (HCV) infection is transmitted through organ transplantation, donors with a positive serology for hepatitis C virus (HCVD+) are included in the latter group[6-12]. Controversies regarding the safety of transplanting kidneys from HCVD+ have been overcome at least partially in the last years through the evidence provided by center-based experiences. However, some centers do not accept kidneys from HCVD+ for transplantation yet. Moreover, there are countries with technical or legal provisions in place that preclude the transplantation of organs from these donors[13]. In parallel, progress in the therapeutic approach to end-stage renal disease patients with an HCV infection raises doubts about the usefulness of policies for the transplantation of kidneys from HCVD+. This article intends to provide an update on the facts about the use of kidneys from these donors and the related challenges for the coming years.

Transmission of HCV infection through kidney transplantation

Soon after the description of HCV in 1989[14], several units published their experiences in the transplantation of kidneys from HCV RNA-positive donors[6-12,15]. The HCV infection was transmitted through kidney transplantation, although the rate of transmission ranged between 14[10] and 100%[8], depending on the series. Moreover, the clinical consequences of the transmission of HCV infection were also variable. Pereira, et al.[8] showed that 50% of the patients acquiring HCV infection through kidney transplantation developed criteria of chronic liver disease (CLD), something otherwise infrequent in the experience of the Columbus University[12]. Variability among the series with regards to the viral load in the transplanted organ, the infectivity of the HCV strain involved, the volume of the preservation solution, the preservation method used, and the diagnostic tests applied might justify these heterogeneous results[9,16].

These experiences lead to the general consensus that kidneys from HCVD+, regardless of HCV RNA, should not be transplanted into recipients with a negative HCV serology (HCVR–)[16]. In parallel, the question to be answered was whether these organs could be safely transplanted into HCVR+. There were arguments against this approach: (i) anti-HCV antibodies are not protective and not indicative of a viremic state, and (ii) several HCV genotypes have been described, so superinfection with another HCV genotype could potentially occur[17]. But there were also strong arguments in favor of this policy: (i) the prevalence of HCV antibodies among organ donors may be high in specific countries or geographical areas, so universally discarding these organs could exacerbate organ shortage; (ii) cardiovascular-related rather than liver-related morbidity and mortality is by far the most frequent after kidney transplantation; and (iii) there is still today a residual risk of discarding a donor with a false positivity for HCV antibodies.

Experiences with the use of kidneys from HCV-positive donors into HCV-positive recipients

Based on the abovementioned arguments in favor of their use, in March 1990 two Spanish kidney transplant units initiated a

pilot experience with the transplantation of kidneys from HCVD+ into HCVR+. First results revealed the short-term safety of this policy. Graft and patient survival of HCVR+ was similar regardless of HCV serology of their donors. A similar percentage of patients in both groups developed biochemical criteria consistent with CLD (ALT levels > 2.5 times the upper normal limit during more than six consecutive months)[18,19]. Nonetheless, the policy did not prevent the transmission of HCV infection. Retrospectively, HCV RNA was assessed in donors and recipients through the polymerase chain reaction (PCR) technique. Three different situations were described when using kidneys from HCVD+ into HCVR+[19]. First, when HCV RNA was detectable in both the donor and the recipient, no negative clinical consequences were apparent in the posttransplant period. As expected, also no negative consequences were observed if the donor was HCV RNA negative and the recipient exhibited a positive HCV RNA. The situation to be avoided was when the donor was HCV RNA positive and the recipient HCV RNA negative, a circumstance described in five patients within the series. Four of them became HCV RNA positive after transplantation and two developed CLD, as previously defined. As a result of these findings, in March 1993 both Spanish groups modified their policy of using kidneys from HCVD+ by limiting their use to those patients in the waiting list who exhibited a positive HCV RNA before transplantation. This approach was then nationally adopted with the support of the Spanish National Transplant Organization.

Other single-center experiences with the same approach as the Spanish one have later been published (Table 1)[20-25]. Conclusions are rather similar among these groups: no outstanding differences are observed in HCVR+ who have received a kidney transplant from an HCVD+ compared to those transplanted from an HCVD-, at least in the short term. Moreover, some of these series have demonstrated that time in the waiting list for HCVR+ is significantly shorter when these patients are transplanted from HCVD+[21,22,24]. Furthermore, according to these experiences in kidney transplantation, livers from HCVD+ have been transplanted into HCVR+ with good results[26].

The information derived from these previously described experiences have been the basis for international guidelines and recommendations on the use of kidneys from HCVD+ for transplantation in a safe way, avoiding their loss at a moment of organ shortage[27-29].

In contrast to the positive results obtained in center-based experiences, registry studies have offered contradictory results. By using the U.S. Renal Data System registry, Abbot, et al. evaluated the outcome of recipients transplanted from HCVD+ versus HCVD-[30,31]. No apparent differences were noticed in terms of graft survival. However, patient survival was significantly worse in recipients transplanted from HCVD+, irrespective of HCV serology of the recipient. The increased risk of death among recipients of HCVD+ kidneys was delayed for two years, which suggested the development of an intermediate complication that resulted in a later increased risk of death[32]. The observed higher incidence of posttransplant diabetes mellitus (PTDM) among recipients of kidneys from HCVD+ could be the reason behind this[32]. These data made the authors conclude that caution should be paid to the use of organs from HCVD+ and that careful and complete information should be provided to the potential recipient of these organs before transplantation[33]. However, when taking a careful look at these papers it is important to note that kidneys from HCVD+ had been used into patients with a worse baseline clinical and immunological situation compared to recipients of kidneys from HCVD-. Factors associated with the use of kidneys from HCVD+ were advanced donor and recipient age, African American race, and a high rate of dialysis

Table 1. Main results of the center-based experiences with the use of kidneys from HCV-positive versus HCV-negative donors in HCV-positive recipients

	Ali[20]		Kasprzyk[25]		Mandal[21]		Morales[35]		Veroux[24]		Woodside[22]	
	D+/R+	D-/R+	D+/R+	D-/R+	D+/R+	D-/R+	D+/R+	D-/R+	D+/R+	D-/R+	D+/R+	D-/R+
Number	28	16	60	199	19	10	162	306	28	16	20	20
Follow-up (months)	36 (12-60)		12-156		15.4 (SD = 2)		74.5		23		26.3	34.9
Acute rejection	50%	68%	–		42%	50%	42.1%	37.2%	10%	14.2%	20%	25%
Graft survival	86%		78%	70%	89%	70%	47% (10 yr)	58.5% (10 yr)	90%	88%	89% (1 yr)	79% (1 yr)
Patient survival	86%		95%	85%	89%	90%	72.7%	76.5%	100%	94%	89% (1 yr)	94% (1 yr)
Acute liver dysfunction	16%*		–	–	16%‡	10%‡	16.1%*	11.6%*	–	–	–	–
Chronic liver dysfunction	9%†				11%§	10%§	9.8%¶	6.2%¶	–	–	–	–
Time in the waiting list (months)	–	–	–	–	9 (SD = 3)**	29 (SD = 3)**	–	–	9	24	9.9 (SD = 1.8)**	17.8 (SD = 3.3)**

D: donor; R: recipient; SD: standard deviation.
*ALT > 2.5 times the upper normal limit for more than 2 weeks, but less than 6 months.
†ALT > 2.5 times the upper normal limit for more than 6 consecutive months.
‡ALT > 2 times the upper normal limit.
§ALT > 2 times the upper normal limit for more than 3 months.
¶Decompensated liver disease: At least one episode of ascites, hepatic encephalopathy and/or gastrointestinal bleeding due to ruptured gastrointestinal varices.
**$p < 0.05$.

access complications[31,32]. It is also important to note that the previously described studies reflected a lack of a specific policy on the use of organs from HCVD+, since they were also used into HCVR-, and there was no information available on the HCV RNA status of the recipients at the time of transplantation. Finally, also by using the U.S. Renal Data System registry, it has been shown that receiving a kidney from an HCVD+ is independently associated with improved patient survival compared with remaining in the waiting list (adjusted HR: 0.76; 95% CI: 0.60-0.96)[34].

Latest evidence on the safety of transplanting kidneys from HCVD+ into HCVR+ has been offered by the Spanish groups piloting the first experiences (Table 1)[35]. For the very first time, information has been offered on the long-term outcome (mean follow-up 74.5 months) of 162 HCVR+ transplanted from HCVD+ (group 1) versus 306 HCVR+ transplanted from HCVD- (group 2). No differences were observed in patient survival. Only three deaths in group 1 and two deaths in group 2 were liver disease related. On the contrary, there was a trend towards a lower death-censored graft survival and a significantly lower non censored for death graft survival in patients transplanted from HCVD+. This could be due to differences in baseline demographic and clinical variables: group 1 exhibited a higher donor and recipient age and, as expected, a more frequent recipient pretransplant viremic state (HCV RNA positive), resulting from the allocation policy applied since 1993. This theory is supported by Mahmoud, et al. who have described a higher frequency

Table 2. Factors independently associated to patient death, graft loss, and decompensated chronic liver disease in the multivariate analysis performed in the Spanish experience[35]

	Patient death*			Graft loss*			Decompensated CLD†		
	P	OR	95% CI	P	OR	95% CI	P	OR	95% CI
HCVD+	0.22	0.709	0.412-1.223	0.18	1.248	0.902-1.726	0.92	1.048	0.429-2.560
Donor age	–	–	–	< 0.001	1.022	1.012-1.032	–	–	–
Recipient age	< 0.001	1.075	1.049-1.102	–	–	–	–	–	–
PRA ≥ 50%	–	–	–	< 0.001	1.912	1.367-2.674	–	–	–
Pretransplant cardiovascular disease	0.05	1.850	0.997-3.432	–	–	–	–	–	–
Delayed graft function	–	–	–	0.03	1.417	1.031-1.949	–	–	–
Acute rejection	–	–	–	< 0.001	1.778	1.304-2.425	–	–	–
NODAT	0.003	2.883	1.447-5.746	–	–	–	–	–	–
Moderate CLD‡	–	–	–	–	–	–	< 0.001	9.462	3.887-23.030
Decompensated CLD§	0.03	2.883	1.447-5.746	–	–	–	–	–	–

CLD: chronic liver disease; HCVD+: positive serology for HCV; PRA: panel-reactive antibody; NODAT: new onset diabetes after transplantation.
*Cox regression analysis.
†Logistic regression analysis.
‡ALT > 2.5 times the upper normal limit for more than 6 consecutive months.
§At least one episode of ascites, hepatic encephalopathy and/or gastrointestinal bleeding due to ruptured gastrointestinal varices.

of chronic allograft nephropathy among HCV RNA-positive recipients[36]. Nevertheless, the Cox-regression analysis performed in the Spanish experience (Table 2) could not identify the donor HCV-positive serology as a significant risk factor for death or graft loss**.** Moreover, decompensated CLD (at least one episode of ascites, hepatic encephalopathy and/or gastrointestinal bleeding due to ruptured gastrointestinal varices) occurred in 10.3 vs. 6.2% of the patients (p = ns), respectively in both groups. Donor HCV-positive serology was not an independent risk factor for the evolution towards a situation of advanced liver disease, as previously defined (Table 2). Although *de novo* PTDM occurred more frequently in group 1, HCVD+ was not identified as an independent risk factor in the multivariate analysis. No differences were observed in the incidence of posttransplant glomerular disease between the two groups.

Limitations of this latest experience are challenges for research in the near future:

- Information on HCV RNA among HCVD+ was lacking, but the practice of testing donors with nucleic acid testing has only been recently suggested[27]. Knowledge about the HCV RNA of donors, however, should not substantially modify the allocation strategy applied to the use of kidneys from HCVD+.

- No information has been provided on the HCV genotype of both donors and recipients, something important to evaluate the incidence of superinfection and its consequences.

- Information on the evaluation of HCV liver disease has been assessed clinically but not histologically. Because liver biopsies were not routinely performed in the series, whether the histological outcome of HCV-related liver disease is different (stable or progressive liver fibrosis)[37] in HCVR+ transplanted from HCVD+ versus HCVD- still remains to be answered.

Decreasing the risk of HCV transmission when using kidneys from HCV-positive donors into HCV-positive recipients

As demonstrated by the Spanish groups, the policy of transplanting kidneys from HCVD+ into HCVR+ does not completely prevent the transmission of HCV infection. Hence, this option should be limited to those candidates for kidney transplantation with a positive HCV RNA in the waiting list. This means that patients with a positive serology for HCV and a positive HCV RNA are the ones to be offered the possibility of receiving a kidney from an HCVD+, always with appropriate information on the special characteristics of these potential donors.

In a very elegant exercise, Natov and Pereira analyzed the consequences of four different approaches to the use of kidneys from HCVD+[38]. The following assumptions were made: 2.4% prevalence of HCV antibodies among deceased donors, second generation ELISA test with 100% sensitivity and 98% specificity, 100% transmission of infection with the use of kidneys from HCV RNA-positive donors, 20% prevalence of HCV infection among patients under dialysis therapy, and absence of clinical consequences of HCV superinfection. No restriction on the use of organs from HCVD+ (all organs used irrespective of HCV serology of the recipients) would be related to 0% of graft losses, but 2.4% of transmission of the infection and 2% of new infections. With a universal restriction on the use of these organs (no organ used irrespective of HCV serology of the recipient), no transmission or new infection would occur but 4.2% of organs would be lost. By using organs from HCVD+ into HCVR+, 0% of graft losses would occur but a risk of transmission (2.4%) and new infection (0.5%) would persist. The best balance seemed to be achieved with the restriction of organs from these donors to recipients with a positive HCV RNA before transplantation, with a theoretical occurrence of 2.4% of transmission of HCV infection but 0% of new infections and no graft losses.

Therefore, the policy of using kidneys from HCVD+ into HCVR+ seems to be safer when the organs are exclusively placed into recipients with a positive HCV RNA before transplantation. But superinfection with a different HCV genotype may still occur. Studies in a posttransfusion hepatitis C infection model in chimpanzees have demonstrated that a preexisting infection with HCV did not protect from reinfection with a different genotype or even the same viral genotype[39]. Likewise, kidney transplant patients with a baseline HCV infection are not protected from a superinfection with a new HCV genotype[17]. Although mixed infection has not been associated with an increased mortality in a recent study[40], at least one clinical report on a severe liver disease has been published when using a kidney from an HCVD+ into an HCVR+, when donor and recipient were infected by a different HCV genotype (genotype 1 to genotype 2)[41]. Therefore, matching donor and recipient according to the HCV genotypes involved should still improve results by reducing the risk of HCV transmission, although limited by obvious time constraints. Besides, depending on the HCV genomic heterogenicity within a specific geographical area, the possibilities of a mismatch between donor and recipient should be balanced.

Is there a place today for the use of HCV-positive donors into HCV-positive recipients: making this policy compatible with interferon therapy before transplantation

It has been documented that survival of HCVR+ is significantly better than that of matched patients who remain in the waiting list[34,42,43]. Therefore, kidney transplantation is

the best therapy for patients with HCV infection and end-stage renal disease. However, HCVR+ have proven to exhibit a worse long-term graft and patient survival than HCVR-[44-50]. Also, HCV infection has been related to the development of posttransplant complications, such as *de novo* PTDM[51], posttransplant glomerulonephritis[52-54], proteinuria and chronic allograft nephropathy[55], after kidney transplantation.

Notably, treatment with interferon (IFN) before kidney transplantation may be related to a decreased incidence of posttransplant HCV-related glomerulonephritis[56]. Interferon therapy in 50 HCV RNA-positive patients significantly decreased the incidence of chronic allograft nephropathy[57]. In spite of this, treatment with IFN before transplantation in HCV-infected patients has not been related yet to benefits in terms of graft or patient survival.

The problem of anti-HCV therapy is that IFN increases the risk of allograft dysfunction and therefore its use in kidney transplant patients is contraindicated, with the exception of patients with fibrosing cholestatic hepatitis[15,27,58,59]. Therefore, the best strategy is to treat HCV infection in patients on dialysis before transplantation[15,27,52,58-62]. While in the past recommendations on end-stage renal disease patients with HCV infection were based on the liver clinical and histological situation[15], the negative clinical consequences of HCV infection after kidney transplantation constitute the basis to indicate therapy with IFN, independently of the stage of the liver disease, in order to improve the outcomes after transplantation[27].

Treatment of HCV infection before transplantation with the aim of a sustained virologic response is obviously not compatible with the use of HCVD+ into HCVR+. However, the limitations of HCV antiviral therapy should be taken into consideration: a wide range of adverse events has been described with IFN therapy, the rate of nonresponding patients is not negligible[63,64], the treatment is long and during this time the patients should be excluded from the waiting list, and finally it is an expensive treatment not universally affordable. Therefore, a group of end-stage renal disease HCV RNA-positive patients would not be candidates for antiviral treatment, some will refuse to be treated, or will not respond or withdraw the therapy. These patients, despite presenting a positive HCV RNA before transplantation should be placed into the waiting list since their outcome will be better than remaining under dialysis[34,65-67]. It is in this context where the possibility of being transplanted with a kidney from an HCVD+ could be offered, with the potential advantage of reducing the time in the waiting list. Even the possibility of preemptive kidney transplantation with organs from HCVD+ for these recipients could be offered. The rationale behind this is simple. The prevalence and the incidence of HCV infection is decreasing among patients with end-stage renal disease. The number of HCV RNA-positive patients in the list is progressively less and most of them are immunologically high-risk patients. Hence, there are a number of kidneys from HCVD+ which are not transplanted because of the lack of an appropriate recipient. Organizational measures should hence be developed in order to allow preemptive transplantation in these exceptional cases.

Finally, some countries may probably not consider the universal approach of treating HCV RNA-positive patients under dialysis because of economic reasons. Unfortunately, these countries are usually those with a higher prevalence of HCV infection among their donors and their recipients. The policy of using HCVD+ for HCVR+ could be a safe approach in these populations.

Conclusions

The use of kidneys from HCVD+ into HCVR+ seems to be a safe approach in the long term and a way of using these kidneys

that otherwise would be lost. Results provided by center-based experiences show a favorable outcome of HCVR+ in terms of graft survival, patient survival, and HCV-related liver disease when transplanted from HCVD+. Registry studies have raised doubts on safety but do not represent a standardized policy. The safety of this approach can be improved by limiting the transplantation of these kidneys to patients with a positive HCV RNA before transplantation and, ideally, by matching donors and recipients according to their HCV genotype. Donor HCV-positive kidneys are being lost today because of remaining doubts that seem to be reasonably overcome nowadays and by the lack of appropriate recipients. Organizational measures such as devising preemptive transplantation for HCV RNA-positive recipients accepting to be transplanted with HCVD+ kidneys and international cooperation seem essential to avoid the loss of these organs at a moment of dramatic organ shortage.

References

1. Global Observatory on Donation and Transplantation. Available at: http://www.transplant-observatory.org/pages/home.aspx. Last access: November 2010.
2. International figures on donation and transplantation 2009. Newsletter Transplant. 2010;15. Website of the Organización Nacional de Trasplantes. Avaialable at: http://www.ont.es/publicaciones/Documents/Newsletter2010.pdf. Last access: November 2010. ***Most comprehensive publication on international donation and transplantation activities.*
3. Organ Procurement and Transplant Network website. Available at: http://optn.transplant.hrsa.gov/latestData/step2.asp? Last access: November 2010.
4. Steering Committee of the Istanbul Summit. Organ trafficking and transplant tourism and commercialism: the Declaration of Istanbul. Lancet. 2008;372:5-6. ***Land-mark reference international professional statement on organ trafficking.*
5. Port FK, Bragg-Gresham JL, Metzger RA, et al. Donor characteristics associated with reduced graft survival: an approach to expanding the pool of kidney donors. Transplantation. 2002;74:1281-6. ***Key reference on the definition of expanded criteria donor based on the analysis of UNOS data.*
6. Pereira BJG, Milford EL, Kirkman RL, Levey AS. Transmission of hepatitis C virus by organ transplantation. N Engl J Med. 1991;325:454-60.
7. Diethelm AG, Roth D, Ferguson RM, et al. Transmission of HCV by organ transplantation. N Engl J Med. 1992; 326:410-11.
8. Pereira BJG, Milford EL, Kirkman RL. Prevalence of HCV RNA in hepatitis C antibody-positive cadaver organ donors and their recipients. N Engl J Med. 1992;327:910-15.
9. Roth D, Fernandez JA, Babischkin S, et al. Detection of hepatitis C infection among organ donors: evidence for low transmission of disease. Ann Intern Med. 1992;117:470-5.
10. Vincenti F, Lake J, Wright T, Kuo G, Weber P, Stempel C. Nontransmission of hepatitis C from cadaver kidney donors to transplant recipients. Transplantation. 1993;55:674-5.
11. Aeder MI, Shield CF, Tegtmeier GE, et al. Incidence and clinical impact of hepatitis C virus (HCV) positive donors in cadaveric transplantation. Transplant Proc. 1993;25:1469-71.
12. Tesi RJ, Waller K, Morgan CJ, et al. Transmission of hepatitis C by kidney transplantation: the risks. Transplantation. 1994;57:826-31.
13. DOPKI WP 5 Statistical analysis. Pages: 155-72. DOPKI website. Available at: http://www.dopki.eu/dmdocuments/WP5_Statistical%20Report.pdf. Last access: November 2010.
14. Choo QL, Kuo G, Weiner AJ, Overby LR, Bradley DW, Houghton M. Isolation of a cDNA clone derived from a blood-borne non-A, non-B viral hepatitis genome. Science. 1989;88:359-62.
15. Morales JM, Campistol JM. Transplantation in the patient with hepatitis C. J Am Soc Nephrol. 2000;11:1343-53.
16. Morales JM, Rodicio JL. Should hepatitis C positive donors be accepted for renal transplantation? Curr Opin Nephrol Hypertens. 1996;5:199-201.
17. Widell A, Mansson S, Persson NH, Thysell H, Hermodsson S, Blohme I. Hepatitis C superinfection in hepatitis C virus (HCV) infected patients transplanted with an HCV infected kidney. Transplantation. 1995;60:642-7.
18. Morales JM, Andres A, Campistol JM. Hepatitis C virus and organ transplantation. N Engl J Med. 1993;328:511-12.
19. Morales JM, Campistol JM, Castellano G, et al. Transplantation of kidneys from donors with hepatitis C antibody into recipients with pre-transplantation anti-HCV. Kidney Int. 1995;47:236-40. **First comprehensive study on the short-term results of transplantation of kidneys from hepatitis C antibody positive donors into hepatitis C positive recipients.*
20. Ali MK, Light JA, Barhyte DY, et al. Donor hepatitis C virus status does not adversely affect short-term outcomes in HCV+ recipients in renal transplantation. Transplantation. 1998;66:1694-7.
21. Mandal AK, Kraus ES, Samaniego M, et al. Shorter waiting times for hepatitis C virus seropositive recipients of cadaveric renal allografts from hepatitis C virus seropositive donors. Clin Transplant. 2000;14:391-6.
22. Woodside KJ, Ishihara K, Theisen JE, et al. Use of kidneys from hepatitis C seropositive donors shortens waitlist time but does not alter one-yr outcome. Clin Transplant. 2003;17:433-7.
23. Veroux P, Veroux M, Puliatti C, et al. Kidney transplantation from hepatitis C virus-positive donors into hepatitis C virus-positive recipients: a safe way to expand the donor pool? Transplant Proc. 2005;37:2571-3.
24. Veroux P, Veroux M, Sparacino V, et al. Kidney transplantation from donors with viral B and C hepatitis. Transplant Proc. 2006;38:996-8.
25. Kasprzyk T, Kwiatkowski A, Wszola M, et al. Long-term results of kidney transplantation from HCV-positive donors. Transplant Proc. 2007;39:2701-3.
26. Testa G, Goldstein RM, Netto G, et al. Long-term outcome of patients transplanted with livers from hepatitis C-positive donors. Transplantation. 1998;65:925-9.
27. Kidney Disease: Improving Global Outcomes. KDIGO clinical practice guidelines for the prevention, diagnosis, evaluation, and treatment of Hepatitis C in chronic kidney disease. Kidney Int. 2008;73(Suppl 109):S1-99. **KDIGO evidence-based guidelines for a holistic approach to the patient with kidney disease and hepatitis C virus infection.*
28. Covic A, Abramowicz D, Bruchfeld A, et al. Endorsement of the Kidney Disease Improving Global Outcomes (KDIGO) hepatitis C guidelines: a European Renal Best Practice (ERBP) position statement. Nephrol Dial Transplant. 2009;24:719-27.
29. Gordon CE, Balk EM, Becker BN, et al. KDOQI US commentary on the KDIGO clinical practice guideline for the prevention, diagnosis, evaluation and treatment of hepatitis C in CKD. Am J Kid Dis. 2008;52:811-25.
30. Bucci JR, Matsumoto CS, Swanson SJ, et al. Donor hepatitis C seropositivity: clinical correlates and effect on early graft and patient survival in adult cadaveric kidney transplantation. J Am Soc Nephrol. 2002;13:2974-82.
31. Abbott KC, Bucci JR, Matsumoto CS, et al. Hepatitis C and renal transplantation in the era of modern immunosuppression. J Am Soc Nephrol. 2003;14:2908-18. ***UNOS registry based study observing an increased mortality among kidney recipients transplanted from donors with a positive serology for hepatitis C.*

32. Bucci JR, Lentine KL, Agodoa LY, Peters TG, Schnitzler MA, Abbott KC. Outcomes associated with recipient and donor hepatitis C serology status after kidney transplantation in the United States: analysis of the USRDS/UNOS database. Clin Transpl. 2004;51-61.
33. Abbott KC. Response to "Viral Hepatitis Guidelines for Transplant Recipients". Am J Transplant. 2005;5:1577-8.
34. Abbott KC, Lentine KL, Bucci JR, Agodoa LY, Peters TG, Schnitzler MA. The impact of transplantation with deceased donor hepatitis C-positive kidneys on survival in wait-listed long-term dialysis patients. Am J Transplant. 2004;4:2032-7.
35. Morales JM, Campistol JM, Domínguez-Gil B, et al. Long-term experience with kidney transplantation from Hepatitis C positive donors into Hepatitis C positive recipients. Am J Transplant. 2010;11:2453-62. **Most comprehensive study on the long-term outcome of kidney recipients transplanted from donors with a positive serology for hepatitis C into recipients with a hepatitis C positive serology.*
36. Mahmoud IM, Elhabashi AF, Elsawy E, El-Husseini AA, Sheha GE, Sobh MA. The impact of hepatitis C virus viremia on renal graft and patient survival: a 9-year prospective study. Am J Kid Dis. 2004;43:131-9.
37. Kamar N, Rostaing L, Selves J, et al. Natural history of hepatitis C virus-related liver fibrosis after renal transplantation. Am J Transplant. 2005;5:1704-12.
38. Natov SN, Pereira BJG. Transmission of viral hepatitis by kidney transplantation: donor evaluation and transplant policies (Part 2: hepatitis C virus). Transpl Infect Dis. 2002;4:124-31.
39. Farci P, Alter HJ, Govindarajan S, et al. Lack of protective immunity against reinfection with hepatitis C virus. Science. 1992;258:135-40.
40. Natov SN, Lau JY, Ruthazer R, Schmid CH, Levey AS, Pereira BJ. Hepatitis C virus genotype does not affect patient survival among renal transplant candidates. The New England Organ Bank Hepatitis C Study Group. Kidney Int. 1999;56:700-6.
41. Schussler T, Staffeld-Coit C, Eason J, Nair S. Severe hepatitis C infection in a renal transplant recipient following hepatitis C genotype mismatch transplant. Am J Transplant. 2004;4:1375-8.
42. Pereira BJ, Levey AS. Hepatitis C virus infection in dialysis and renal transplantation. Kidney Int. 1997;51:981-99.
43. Knoll GA, Tankersley MR, Lee JY, Julian BA, Curtis JJ. The impact of renal transplantation on survival in hepatitis C positive end-stage renal disease patients. Am J Kidney Dis. 1997;29:606-14.
44. Morales JM, Domínguez-Gil B, Sanz-Guajardo D, Fernandez J, Escuin F. The influence of hepatitis B and hepatitis C virus infection in the recipient on late renal allograft failure. Nephrol Dial Transplant. 2004;19(Suppl 3):72-6.
45. Legendre C, Garrigue V, Le Bihan C, et al. Harmful long-term impact of hepatitis C virus infection in kidney transplant recipients. Transplantation. 1998;65:667-70.
46. Mathurin P, Mouquet C, Poynard T, et al. Impact of hepatitis B and C virus on kidney transplantation outcome. Hepatology. 1999;29:257-63.
47. Gentil MA, Rocha JL, Rodríguez-Algarra G, et al. Impaired kidney transplant survival in patients with antibodies to hepatitis C virus. Nephrol Dial Transplant. 1999;14:2455-9.
48. Breitenfeldt MK, Rasenak J, Berthold H, et al. Impact of hepatitis B and C on graft loss and mortality of patients after kidney transplantation. Clin Transplant. 2002;16:130-6.
49. Aroldi A, Lampertico P, Montagnino G, et al. Natural history of hepatitis B and C in renal allograft recipients. Transplantation. 2005;15:1132-6.
50. Fabrizi F, Martin P, Dixit V, Bunnapradist S, Dulai G. Hepatitis C virus antibody status and survival after renal transplantation: meta-analysis of observational studies. Am J Transplant. 2005;5:1452-61. **Metanalysis on observational studies demonstrating a significant negative impact of hepatitis C virus antibody status on graft and patient survival after kidney transplantation.*
51. Fabrizi F, Martin P, Dixit V, Bunnapradist S, Kanwal F, Dulai G. Posttransplant diabetes mellitus and HCV seropositive status after renal transplantation: meta-analysis of clinical studies. Am J Transplant. 2005;5:2433-40.
52. Cruzado JM, Gil-Vernet S, Ercilla G, et al. Hepatitis C virus-associated membranoproliferative glomerulonephritis in renal allografts. J Am Soc Nephrol. 1996;7:2469-75.
53. Roth D, Cirocco R, Zucker K, et al. De novo membranoproliferative glomerulonephritis in hepatitis C virus-infected renal allografts recipients. Transplantation. 1995;59:1676-82.
54. Morales JM, Pascual-Capdevila J, Campistol JM, et al. Membranous glomerulonephritis associated with hepatitis virus infection in renal transplant patients. Transplantation. 1997;63:1634-9.
55. Hestin D, Guillemin F, Castin N, Le Faou A, Champigneulles J, Kessler M. Pre-transplant hepatitis C virus infection: a predictor of proteinuria after renal transplantation. Transplantation. 1998;65:741-4.
56. Cruzado JM, Casanovas-Taltabull T, Torras J, Baliellas G, Gil-Vernet S, Grinyo JM. Pretransplant Interferon prevents hepatitis C virus- associated glomerulonephritis in renal allografts by HCV-RNA clearance. Am J Transplant. 2003;3:357-60. ***Elegant series on the impact of interferon treatment before transplantation on a decreased incidence of hepatitis C-related glomerulonephritis after kidney transplantation.*
57. Mahmoud IM, Sobh MA, El-Habashi AF, et al. Interferon therapy in hemodialysis patients with chronic hepatitis C: study of tolerance, efficacy and posttransplantation course. Nephron Clin Pract. 2005;100:c133-9.
58. Kamar N, Ribes D, Izopet J, Rostaing L. Treatment of hepatitis C virus infection (HCV) after renal transplantation: implications for HCV-positive dialysis awaiting a kidney transplant. Transplantation. 2006;82:853-6.
59. Fabrizi F, Lunghi G, Dixit V, Martin P. Meta-analysis: antiviral therapy of hepatitis C virus-related liver disease in renal transplant patients. Aliment Pharmacol Ther. 2006;24:1413-22.
60. Campistol JM, Esforzado N, Morales JM. Hepatitis C virus-positive patients on the waiting list for renal transplantation. Semin Nephrol. 2002;22:361-4.
61. Rostaing L, Chatelut E, Payen JL, et al. Pharmacokinetics of alfaIFN-2b in chronic hepatitis C virus patients undergoing chronic haemodialysis or with normal renal function: clinical implications. J Am Soc Nephrol. 1998;9:2344-8.
62. Kamar N, Toupamce O, Buchler M, et al. Evidence that clearance of hepatitis C virus RNA after alpha interferon therapy in dialysis patients is sustained after renal transplantation. J Am Soc Nephrol. 2003;14:2092-8.
63. Fabrizi F, Dixit V, Messa P, Martin P. Pegylated interferon monotherapy of chronic hepatitis C in dialysis patients: Meta-analysis of clinical trials. J Med Virol. 2010;82:768-75.
64. Gordon CE, Uhlig K, Lau J, Schmid CH, Levey AS, Wong JB. Interferon for hepatitis C virus in hemodialysis--an individual patient meta-analysis of factors associated with sustained virological response. Clin J Am Soc Nephrol. 2009;4:1449-58.
65. Knoll GA, Tankersley MR, Lee JY, et al. The impact of renal transplantation on survival in hepatitis C-positive end-stage renal disease patients. Am J Kidney Dis. 1997;29:608-14.
66. Pereira BJ, Natov SN, Bouthot BA, et al. Effects of hepatitis C infection and renal transplantation on survival in end-stage renal disease. The New England Organ Bank Hepatitis C Study Group. Kidney Int. 1998;53:1374-81.
67. Bloom RD, Sayer G, Fa K, et al. Outcome of hepatitis C virus-infected kidney transplant candidates who remain on the waiting list. Am J Transplant. 2005;5:139-44.