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REVIEW

Hepatitis C virus infection in end-stage renal disease and kidney transplantation

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Summary

Liver disease secondary to chronic hepatitis C virus (HCV) infection is an important cause of morbidity and mortality in patients with end-stage renal disease (ESRD) on renal replacement therapy and after kidney transplantation (KT). Hemodialytic treatment (HD) for ESRD constitutes a risk factor for bloodborne infections because of prolonged vascular access and the potential for exposure to infected patients and contaminated equipment. Evaluation of HCV-positive/ESRD and HCV-positive/KT patients is warranted to determine the stage of disease and the appropriateness of antiviral therapy, despite such treatment is challenging especially due to tolerability issues. Antiviral treatment with interferon (IFN) is contraindicated after transplantation due to the risk of rejection, and therefore, treatment is recommended before KT. Newer treatment strategies of direct-acting antiviral agents in combination are revolutionizing HCV therapy, as a result of encouraging outcomes streaming from recent studies which report increased sustained viral response, low or no resistance, and good safety profiles, including preservation of renal function. KT has been demonstrated to yield better outcomes with respect to remaining on HD although survival after KT is penalized by the presence of HCV infection with respect to HCV-negative transplant recipients. Therefore, an appropriate, comprehensive, easily applicable set of clinical practice management guidelines is necessary in both ESRD and KT patients with HCV infection and HCV-related liver disease.

Introduction—The burden of hepatitis C virus in end-stage renal disease and kidney transplant recipients

According to the World Health Organization, about 150 million people worldwide are chronically infected with hepatitis C virus (HCV) [1]; nearly 6% of patients with end-stage renal disease (ESRD) on conservative therapy [2], between 4% and 70% patients on hemodialysis (HD), and 11–49% kidney transplant (KT) recipients [3–9] are infected with HCV. These are not small numbers, considering that worldwide more than 1.4 million patients are on HD programs [10,11], and approximately 77 8181 KT are performed yearly, according to the Global Observatory on Donation and Transplantation [12].

Epidemiology of HCV in patients with ESRD

Hepatitis C virus infection is highly prevalent among patients with ESRD undergoing HD and remains the main cause of liver disease in this population, although in recent years, the prevalence has been reduced by almost one-third [13,14]. The prevalence varies among different regions, with a higher proportion of infected patients in developing countries (approximately 75–80%) than in developed regions (approximately 3.4%) [15–17].

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A negative trend of the prevalence of anti-HCV positivity in HD patients during the last decade (1991–2000), which was from 28% to 16% in Italy, was reported in a European multicenter study [18]. The prevalence of HCV in HD patients is also related to factors other than local sanitary practices and frequency of infection and transmission, such as the duration of HD. In a study reporting on 151 patients evaluated for KT at a tertiary center, HCV positivity was significantly associated with male gender, African–American origin, being on dialysis, and with more prolonged time on dialysis (30 ± 44 months vs. 13 ± 23 months; $P = 0.0001$, for HCV-negative versus HCV-positive patients, respectively) [19].

Risk factors and prevention of HCV infection in patients with ESRD

A systematic review of 20 studies analyzing possible transmission routes was published in the Kidney Disease: Improving Global Outcomes (KDIGO) Guidelines [20] which was unable to establish the specific route of transmission, and the internal HD machine circuit is, at most, a minor contributor to the nosocomial transmission of HCV among HD patients [21]. Cross-contamination from supplies and surfaces resulting from failure of staff to follow infection-control procedures seems to be the major factor for HCV transmission [20]. The KDIGO guidelines therefore strongly recommend that HD units should ensure implementation of, and adherence to, strict infection-control procedures designed to prevent transmission of bloodborne pathogens, including HCV, whereas isolation of HCV-infected patients is not recommended, neither by KDIGO nor by the Center for Disease Control (CDC). According to the American Association for the Study of Liver Diseases (AASLD) guidelines [22], baseline testing in dialysis patients should include assays for both HBV and HCV infection and serum alanine aminotransferase (ALT) levels. For anti-HCV-negative patients, the recommendation is to monitor ALT levels monthly and anti-HCV every 6 months. Increases in ALT levels should prompt testing for HCV infection, and if anti-HCV is negative despite persistently increased ALT levels, testing for HCV RNA employing, that is, polymerase chain reaction, should be considered [22] and repeated if negative. This is especially important in patients on dialytic therapy, in whom low, fluctuating viremia might be the case, resulting in undetectable viremia despite the presence of the virus.

Diagnosis of HCV infection and liver function assessment in patients with ESRD

Patients with end-stage renal disease represent a special population, in whom markers of liver disease severity are different. Anti-HCV testing may not be reliable given the diminished antibody-forming response that is present in ESRD [23], and HCV-RNA positivity may be observed in the presence of negative anti-HCV antibodies, although this is observed less frequently with third-generation assays. It seems that in this population, the quantitative HCV core antigen (HCVcAg) test that is able to detect total nucleocapsid core antigen, in which sequence is highly conserved across HCV genotypes, may prove to constitute a better screening strategy [24–26].

Moreover, determination of HCV RNA is not intended to be used as screening for detection of HCV infection [27], considering that imperfect handling and/or storage of blood samples can lead to false-negative testing in up to 40% of samples [28], and considering that patients in dialysis often have intermittent viremia or very low levels of HCV RNA, which may all compromise the test's sensibility and may warrant repeat testing [29].

Normal ALT levels are frequent even in the presence of active infection, and levels of this enzyme do not correlate well with hepatic involvement [30]. The same lacking correlation was reported between viremia and histological damage [31,32]. However, when liver biopsy was performed in 30 anti-HCV-positive patients/patients with ESRD, the mean histologic activity scores for inflammation and fibrosis were significantly higher for HCV-RNA-positive compared with HCV-RNA-negative group [33].

HCV-related liver disease in patients with ESRD

The natural history of HCV infection in HD patients tends to have a mild course [34–38]. Several theories have been proposed to explain this generally more indolent course, including the altered immunologic state and the relatively low HCV viral load in the HD population, which could be due to the clearance of HCV RNA by the dialysate and/or the entrapment of HCV-RNA particles within the dialyzer surface membranes [39], and an indirect host-mediated mechanism of production of interferon-alpha (IFN-alpha), hepatocyte growth factor, and other cytokines with antiviral activity may play a role [36,40].

Notwithstanding that, the adverse impact of HCV-related liver disease on mortality in the population with ESRD has been well documented. In a large cohort study pooling over 23 000 patients on HD, although overall 5- and 10-year survival between HCV-positive and HCV-negative patients was similar, the adjusted hazard ratio for mortality was increased (1.25; 95% CI 1.07–1.46) in the former, and liver failure was more likely [41]. Infected patients have a 25% increased risk of mortality on HD compared with HCV-negative counterparts [17,42,43]. The Dialysis Outcomes and Practice Patterns Study (DOPPS), a prospective observational study of representative samples

of HD patients analyzing 16 720 patients from several countries who were followed for up to 5 years, showed an independent and significant association between HCV and mortality (RR, 1.17; $P < 0.0159$) [44]. In a meta-analysis pooling 11 589 patients, it was demonstrated that the presence of anti-HCV antibody was an independent and significant risk factor for death in patients on HD and as a cause of death, hepatocellular carcinoma and cirrhosis were significantly more frequent among HCV-positive than HCV-negative HD patients [45]. Moreover, in a more recent meta-analysis performed by the same work group, including a total of 145 608 HD patients, the presence of anti-HCV antibody was demonstrated to constitute an independent and significant risk factor for death. In fact, the summary estimate for adjusted relative risk was 1.35 with a 95% confidence interval (CI) of 1.25–1.47. Interestingly, not only liver-related deaths (adjusted RR 3.82–95% CI, 1.92; 7.61) but also cardiovascular mortality (adjusted RR 1.26–95% CI, 1.10; 1.45) constituted the causes for the increased mortality observed in HCV-positive patients/patients with ESRD compared with HCV-negative counterparts [46]. Cirrhosis and other liver-related deaths are reported more frequently in HCV-positive/HD patients than in HCV-negative counterparts [47,48]. Figure 1 summarizes the management of HCV-infected patients with ESRD.

Treating HCV infection before KT

The rationale for anti-HCV treatment derives from the fact that in patients with ESRD, HCV infection constitutes an independent predictor of morbidity and mortality due to increased progression to cirrhosis and the development of hepatocellular carcinoma [47,49]. Moreover, after KT, higher mortality and reduced graft survival have been demonstrated in HCV-positive recipients [50,51], in whom IFN treatment is usually contraindicated due to the increased risk of rejection [52–55]. Therefore, it is advisable to treat

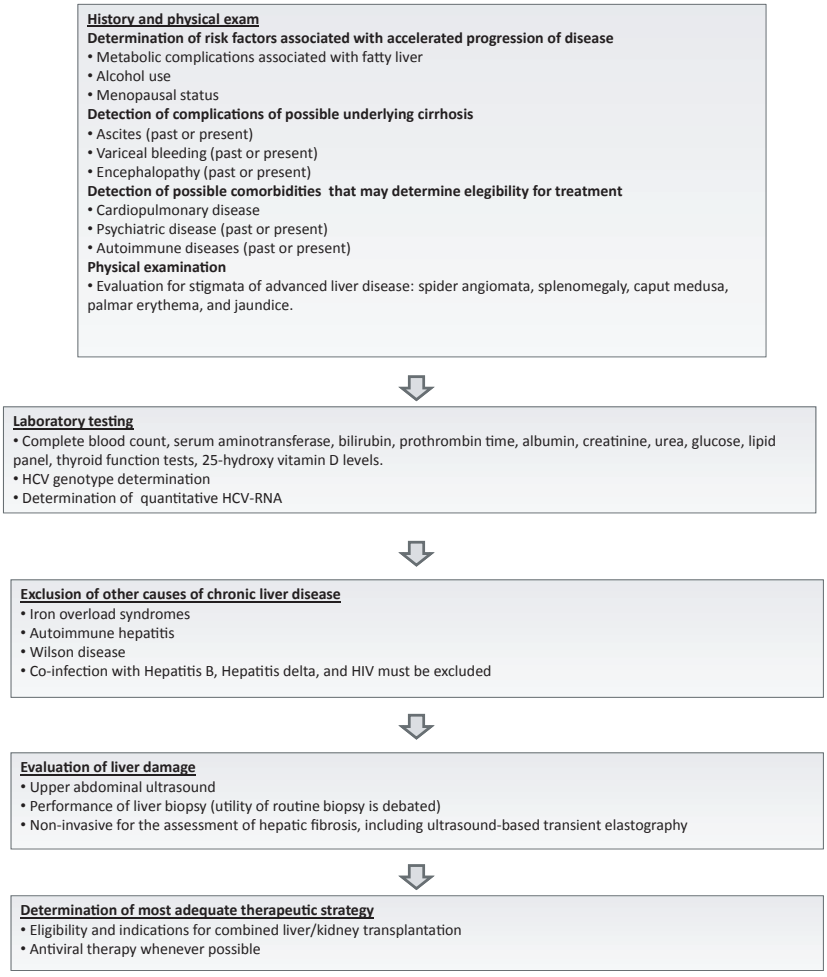

Figure 1 Management of hepatitis C infection in patients with end-stage renal disease.

HCV infection in patients with chronic renal disease prior to KT [56] and estimate the possible risk-benefit balance, including life expectancy and eligibility for KT, as it has been suggested that therapy is likely to be of less benefit in patients with ESRD with life expectancy of <5 years [57]. Treating patients with ESRD in cases in whom KT is foreseen is particularly advised to delay the course of liver disease, reduce the risk of post-transplant complications associated with HCV, and hopefully achieve sustained viral response (SVR), as the outcome of HCV-positive patients after KT is worse than HCV-negative counterparts [58].

Regarding effects of antiviral treatment, the kidneys play a major role in both catabolism and filtration of IFN and ribavirin (RBV) [59], and therefore, their clearances may be affected in subjects with ESRD. RBV's risk of hemolytic anemia, which is proportional to plasmatic levels, is higher in uremic patients due to impaired clearance and could cause life-threatening anemia [60]. This adverse effect may be successfully addressed reducing the dose of RBV and with an increased use of erythropoietin. Furthermore, of note, RBV is not removed by dialysis. Elimination of pegylated interferon (Peg-IFN) is also altered in patients with ESRD, and HD does not affect its clearance [61,62].

According to the most recent KDIGO guidelines [20], which date back to 2008, in patients with glomerular filtration rate (GFR) >50 ml per min per 1.73 m^2, the safety and efficacy of combined IFN and RBV therapy are not compromised by impaired kidney function, with recommended dose of Peg-IFN alpha-2a of 180 μg weekly or Peg-IFN alpha-2b 1.5 μg/kg weekly and RBV 800–1200 mg day in two divided doses, while in patients in grades 3 and 4 of chronic kidney disease, the recommendation is to employ Peg-IFN alpha-2a 135 μg weekly or Peg-INF alpha-2b 1 μg/kg weekly and RBV 400–800 mg day in two divided doses, excluding patients with GFRs of <50 ml per min per 1.73 m^2, in whom RBV is not recommended. Moreover, in HD patients, these guidelines recommend the use of alpha-2a IFN or alpha-2b, 3 mIU 3 times/week, while RBV use is not recommended [20].

The later issued AASLD guidelines [4] differ from the KDIGO guidelines in that the cutoff value for GFR > 60 ml per min for administering the same treatment as that used in patients without kidney disease. Aside from standard interferon, the AASLD guidelines also propose the use of reduced dose Peg-INF alpha-2a to 135 μg weekly or Peg-INF alpha-2b 1 μg/kg weekly, allowing the use of RBV in combination with IFN in a markedly reduced daily dose with careful monitoring for anemia and other adverse effects [22].

Agreement between the two guidelines exists in the post-KT setting, and IFN therapy is not recommended, unless for the treatment of fibrosing cholestatic hepatitis or life-threatening vasculitis [20,22].

Initial treatment strategies in patients with ESRD consisted of conventional or Peg-IFN monotherapy and were associated with low response rates. In a meta-analysis that evaluated the efficacy and safety of this approach, the use of conventional IFN yielded an estimated SVR rate of 39% [95% confidence interval (CI) 32–46], while the use of Peg-IFN yielded an estimated SVR of 31% (95% CI 7–55), with no statistical difference between drugs used and with dropout rates of approximately 20–30% of patients, most frequently due to flu-like symptoms as well as gastrointestinal and hematological alterations [63].

A meta-analysis of 16 clinical trials of HD patients on Peg-INF monotherapy showed a 33% SVR rate, but poor tolerance to the drug, with a 23% dropout rate [64]. A more recent meta-analysis of 28 clinical trials [65] reported an overall SVR of 39% and a dropout rate of 19% when standard interferon therapy was used. Smaller studies have reported higher SVR rates (approximately 50% in patients on HD using standard IFN or Peg-IFN plus low-dose RBV (200 mg/day or 200 mg thrice weekly), provided hemoglobin levels are sustained by erythropoietin and iron therapy [66–69].

Regarding the use of direct antiviral agents (DAAs), telaprevir (TPV) and boceprevir (BOC) have been associated with safety concerns regarding patients with CKD, especially since both BOC and TPV potentiate RBV-associated anemia [42]. An initial study comparing the safety and pharmacokinetics of BOC in HD against healthy patients showed no meaningful alterations in mean maximum plasma concentration, area under the plasma concentration–time curve, nor half-life of this drug, suggesting no need for dose adjustment and also confirming that BOC is not removed by HD [70]. However, the recently conducted, noninterventional PAN study evaluating treatment with Peg-IFN alpha-2a/RBV with or without TPV or BOC in patients with HCV showed that for genotype one patients who completed 12 or 24 weeks of treatment and who had baseline GFR >60 ml/min, patients on TPV (38/575 corresponding to 6.6%) and BOC (10/211 corresponding to 4.7%) more frequently experienced a decrease in estimated GFR to <60 ml/min compared with patients on Peg-INF/RBV (1/109 corresponding to 0.9%), ($P < 0.05$). Substantial RBV dose reductions had to be considered as anemia was shown to be more pronounced in patients with alterations in renal function [71]. In another small study by Dumortier, four HD patients were treated with Peg-IFN, RBV, and TPV, with encouraging outcomes, undetectable HCV RNA in 3 of 4 patients after 12 weeks of triple therapy, and only mild anemia which was managed with increased doses of erythropoietin [72].

Regarding the new antiviral treatments and interferon-free regimens, in the trial using RBV, ABT-450/r, and ABT-333 on an HCV-infected, noncirrhotic population without

baseline renal dysfunction, two of 50 patients presented increase in plasmatic creatinine and new onset creatinine clearance reduction below <50 ml/min, although these alterations resolved spontaneously [73]. Further trials are needed to establish the safety and efficacy of these new agents in HD patients. Table 1 summarizes the most recent studies (meta-analyses and original studies) on different treatment protocols including IFN monotherapy, IFN + RBV combined therapy, and triple therapy with BOC or TPV.

Sofosbuvir, a nucleotide analog inhibitor of HCV NS5B polymerase, has emerged as a valuable agent, not only due to its potent antiviral activity across all genotypes in association with peg-IFN and RBV, but also within IFN-free regimens in terms of safety profile, as no dose adjustment is required for patients with mild or moderate renal impairment. However, the efficacy and safety of this drug have not been established in patients with severe renal impairment (eGFR < 30 ml/min/1.73 m^2) or patients with ESRD requiring HD. Pharmacokinetic studies performed in HCV-negative subjects with renal impairment showed that in subjects with severe renal impairment, sofosbuvir and GS-331007 area under the curve inferior (AUC_{inf}) was 171% and 451% higher, respectively, compared with subjects with normal renal function, and in subjects with ESRD, sofosbuvir AUC_{inf} was 28% higher when dosed 1 h before HD compared with 60% higher when dosed 1 h after HD, which correspond to at least a 10-fold and 20-fold higher, respectively, of that observed in healthy subjects. HD can efficiently remove the predominant circulating metabolite GS-331007 (53% extraction ratio) [74]. As in ESRD, one of the most important adverse effects of traditional therapy with RBV is anemia, which often precludes a successful treatment, emerging agents that do not include this drug could represent a very interesting and relevant alternative in this patient population. Feldaprevir in the SOUND-C2 [75,76], ABT-450/r, ABT-267, ABT-333 in the Aviator study [77], Daclatasvir plus Sofosbuvir [78], Simeprevir plus Sofosbuvir in the COSMOS study [79], and MK-5172 plus MK-8742 in the C-WORTHY study [80] have all included treatment arms without RBV. Potentially, these IFN- and RBV- free regimens might be used in patients on HD to avoid the risk of anemia.

Finally, the severity of liver disease and the presence of other comorbidities must also be taken into consideration before planning treatment. In case of advanced hepatic compromise, antiviral treatment might be contraindicated due to possible hepatic decompensation, and the option of combined liver–kidney transplantation (KT) may represent the most adequate alternative, until we will definitively provide the efficacy and safety of interferon-free and RBV-free antivirals.

HCV in the KT recipient

Prevalence of HCV in KT recipients

The prevalence of HCV infection in KT recipients varies from 6% to 46% [81] and varies according to factors including the specificity and sensibility of the diagnosis tests employed, the prevalence of HCV infection in dialysis units, the type of dialysis (HD versus peritoneal dialysis), and the duration of dialytic therapy previous to KT. In a recent study based on the Australian and New Zealand Dialysis and Transplant registry [41], of a cohort of 7572 KT recipients, 140 (1.8%) were HCV positive, while the respective dialysis cohort (23 046 patients) had a prevalence of 1.6%. Reportedly, 74–92% of KT recipients who are HCV positive have detectable HCV RNA, which persists in the majority of these patients [82]. After KT, levels of HCV-RNA rise, as a consequence of immunosuppressive therapy [83]. In contrast, the percentage of KT recipients who are HCV-RNA positive but are not able to mount an antibody response against HCV and are thus negative for anti-HCV is less clear [84–87]. In most HCV-positive/KT recipients, the infection occurs before transplant, while patients are on HD, whereas only exceptionally has acquisition of HCV infection reported to occur through an infected donor [88] and is infrequently acquired after KT.

KT of grafts from HCV-positive donors

KT from anti-HCV-positive donors to only HCV-RNA-positive recipients is consistent with the recommendations from the KDIGO guidelines [20], and this practice shortens the waiting time for HCV-positive KT candidates without increasing the rate of rejection episodes, infectious complications, graft loss, or mortality [89]. A survey carried out in 147 KT centers in the USA revealed that organs from HCV-positive donors are used in 49% of these centers [90]. No differences in terms of patient survival or development of liver disease have been demonstrated between HCV-positive KT recipients of grafts from HCV-positive donors [91,92]. Considering the several identified HCV genotypes and subtypes, KT recipients with pre-existing HCV infection may develop reinfection (a new infection after a previous infection has theoretically cleared) with the same or a different HCV strain or super infection (infection with a new HCV strain in the presence of current active infection), and after KT, detectable HCV RNA may correspond to that of the donor, that of the recipient, or to both individual's genotypes [93,94]. However, it has been demonstrated that the type of HCV infection (infection with one or more HCV genotypes) does not have an adverse impact on survival in KT recipients [95]. Recently, the case of an HCV-positive patient who was successfully treated with antiviral therapy and 1 year after treatment completion donated a

Table 1. Recent studies evaluating the use of different antiviral therapies, including interferon (IFN) monotherapy, pegylated interferon (PEG-IFN) monotherapy, combined therapy with PEG-IFN and ribavirin (RBV), and triple therapy regimens including telaprevir (TPV) or boceprevir (BOC), in patients with end-stage renal disease and hepatitis C (HCV) infection.

Reference	Publication date	Treated patients (*n*)	Treatment protocol (s)	Outcomes	Adverse events
Meta-analysis studies evaluating IFN in patients with ESRD					
Fabrizi *et al.* [135]	2003	269 (pooled patients)	IFN 3 MU × 3/week SC for 24 weeks	SVR 37% Dropout rate 37%	Antiviral therapy associated with more adverse events in dialysis patients
Russo *et al.* [136]	2003	213 (pooled patients)	IFN 3 MU × 3/week SC for 24 weeks	SVR 33% Dropout rate 29.6%	Antiviral therapy associated with more adverse events in dialysis patients
Studies evaluating the use of PEG-IFN in patients with ESRD					
Russo *et al.* [137]	2006	16	Peg-IFN alpha-2b SC weekly for up to 48 weeks 9 subjects randomized to 1.0 μg/kg and 7–0.5 μg/kg	Study was terminated because of adverse events and need for modifications in the study design SVR in 2 of 9 patients on higher dose SVR in 0 of 7 patients on lower dose	Serious adverse events in 5 of 16 patients (56%); requiring discontinuation of therapy in the 1.0 mcg/kg group and in 2 of 16 (28%) of the 0.5 mcg/kg group Anemia, infection unrelated to neutropenia, hypertension.
Teta *et al.* [138]	2005	3	Peg-IFN alpha-2a 180 mcg SC weekly for 48 weeks 2 of 3 patients with biopsy-proven chronic liver disease 1 of 3 patient with acute HCV hepatitis	SVR in 2 of 3 patients	Anemia, pseudoporphyria cutanea, mixed interstitial and obstructive broncopneumopathy
Peck-Radosavljev *et al.* [139]	2011	85	Peg-IFN Patients were randomized to 135 (38 patients) or 90 mcg/week (43 patients) for 48 weeks No placebo group	SVR in 15 of 38 patients treated with 135 mcg/week and in 15 of 43 patients in the 90 mcg/week group	Anemia, hypertension
Meta-analysis studies evaluating Peg-IFN in patients with ESRD					
Fabrizi *et al.* [65]	2011	151	IFN-alpha2b 3 mIU × 3/week + RBV 170–300 mg/day for 24–28 weeks or PEG-IFN-alpha 2a 135 mcg/week + RBV 130–200 mg/day or × 3/week for 24–48 weeks	SVR 56% Dropout rate 25%	Anemia, heart failure
Studies evaluating Peg-IFN plus ribavirin in patients with ESRD					
Rendina *et al.* [67]	2007	35	35 patients on PEG-IFN alpha-2a 135 mcg/week + RBV 200 mg/day for 24 weeks-48 weeks vs. 35 untreated controls	SVR in 34 of 35 treated patients	Anemia, dermatitis

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Table 1. continued

Reference	Publication date	Treated patients (*n*)	Treatment protocol (s)	Outcomes	Adverse events
Tseng *et al.* [140]	2013	52	26 patients on PEG-IFN alpha-2b 1 mcrg/kg/week and 26 patients on PEG-IFN alpha-2b 1 mcrg/kg/week + RBV 200 mg × 3/week for 24–48 weeks	SVR in 7 of 26 patients on monotherapy and in 16 of 26 patients on combined therapy	Anemia
Alsaran *et al.* [141]	2013	14	PEG-IFN alpha-2b 1 mcg/kg/week + RBV 200 mg × 3/week for 48 weeks	SVR in 9 of 14 patients	Anemia, thrombocytopenia
Liu *et al.* [142]	2013	205	Patients were randomized to Peg-IFN-alpha 2a 135 mcg weekly (102 patients) or Peg-IFN-alpha 2a + RBV 200 mg daily (103 patients) for 48 weeks	SVR in 34 of 102 patients on monotherapy and in 66 of 103 patients on combined therapy	More patients on combination therapy had severe anemia One case of fatal Stevens-Johnson syndrome in a patient on combination therapy
Liu *et al.* [143]	2014	172	Patients were randomized to PEG-IFN-alpha 2a 135 mcg/week (86 patients) or PEF-IFN-alpha 2a 135 mcg/week + RBV 200 mg/day (86 patients)	SVR in 38 of 86 patients on monotherapy and in 64 of 86 patients on combination therapy	Anemia
Studies evaluating triple therapy including telaprevir (TPV) and boceprevir (BOC)					
Dumortier *et al.* [72]	2013	4	Previous nonresponders to Peg-IFN + RBV. All 4 patients received PEG-IFN + RBV + TPV	EVR in 3 of 4 patients	Anemia
Knapstein *et al.* [144]	2014	1	Peg-IFN + RBV + BOC in a patient with chronic HCV infection awaiting kidney retransplantation	HCV negative at week 6	Dysguesia, diarrhea, anemia

SVR, Sustained viral response.

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kidney to an HCV-negative recipient was reported. Although in this case, HCV-RNA status of the recipient was not reported, no clinical manifestations of HCV infection were evident after immunosuppressive post-KT therapy, suggesting that successfully treated HCV infection may not preclude kidney donation to an HCV-negative recipient [96].

Outcome of KT recipients with HCV infection

As it is clear that HCV has a negative impact on survival in HD patients, it has also become evident that although outcomes after KT are worse for HCV-infected individuals with respect to HCV-negative counterparts [97,98], KT still represents a better chance of survival than remaining on HD [51]. A recent meta-analysis pooling 1734 patients with ESRD, pertaining to studies comparing death rates on the waiting list against mortality after KT, albeit evidence of significant heterogeneity of death rates across studies, showed that mortality for HCV-positive patients/patients with ESRD is greater while on the waiting list for KT than after transplantation [99]. Furthermore, the major cause of death while on the waiting list is cardiovascular disease, while after transplantation, it is infection [99]. After KT, ALT levels may increase in those patients with previously normal values as well as increase even more than previously in those in whom this enzyme was already above normal, and HCV viral load tends to increase approximately 1.0–1.5 log10 IU/ml [100,101]. Neither parameter, however, is reliable in the identification of KT recipients with significant histologic damage [102]. Progression to liver fibrosis has been reported to be approximately 36–40%, 3–4 years after KT [103,104], without evidence of a relationship between viral load or genotype and fibrosis progression. Interestingly, in a study performed before KT, viral load and determination of HCV core antigen correlated well with the degree of hepatic histologic compromise, and although after KT, overall mortality and graft loss were not significantly different between HCV-RNA-negative and HCV-RNA-positive patients, progression of liver disease was observed only in the latter [33], suggesting that liver biopsy is probably unnecessary in anti-HCV-positive KT recipients who are HCV-RNA-negative. Ultrasound elastrography (FibroScan), a radiologic technique that employs a modified ultrasound probe to measure the velocity of a shear wave created by a vibratory source [105], is increasingly been used as a noninvasive method to evaluate liver fibrosis in KT patients [106]. Henceforth, serial evaluations using FibroScan can be safely introduced in the evaluation and management practices of HCV-infected KT recipients to monitor the progression of fibrosis in HCV-infected kidney allograft recipients [107].

In a study from our center, Padua University Hospital, 54 anti-HCV-positive KT candidates, of whom 38 were HCV-RNA-positive, were followed from January 1995 to January 2010. The local joint protocol enacted by attending nephrologists, surgeons, and gastroenterologists for the management of KT candidates with HCV infection [108] includes the determination of liver function tests, anti-HCV antibodies, and quantitative HCV RNA before KT, at 1, 6, 12 months after KT, and every year thereafter. Hepatic ultrasound is performed in all patients every 6–12 months before and also after KT. The indication to perform liver biopsy is posed in the presence of HCV-RNA positivity, and histological damage is classified according to Scheuer [109] and Ishak [110]. Based on virological and histological data, every patient is assigned a score that predicts liver disease progression according to the following scheme: *Low risk:* HCV-RNA-negative patients without liver damage; *mild–moderate risk:* HCV-RNA-positive patients of non-1b genotype and moderate chronic hepatitis ($G = 1–2$; $S < 2$); *moderate risk:* HCV-RNA-positive patients of genotype 1b and moderate chronic hepatitis ($G = 1–2$; $S = 2$); *high–moderate risk:* HCV-RNA-positive patients of genotype 1b and severe–moderate chronic hepatitis ($G = 2–3$; $S > 2$); and *high risk:* HCV-RNA-positive patients of genotype 1b and severe–moderate chronic hepatitis ($G = 2–3$; $S > 2$) [108]. In this study, liver biopsy was performed in 29 patients, demonstrating fibrosis F0 in 10, F1 in 10, F2 in 7, and $F \geq 3$ in 2 patients. The local score for predicting the likelihood of liver disease progression demonstrated a low risk in 4, low/intermediate in 7, intermediate in 12, intermediate/high in 4, and high in 2 patients. Eight patients were treated with IFN, obtaining SVR in three individuals. Thirty-eight patients received a KT, and no episodes of hepatitis were detected. The long follow-up (up to 15 years after transplant) in KT recipients showed survival rates which are similar to those of non-HCV patients at our center. In this study, HCV status did not have a negative impact on graft nor patient survival in KT recipients, and the use of a scoring system including histological features and viremia effectively allowed for patient stratification regarding antiviral therapy and prognosis of liver disease.

Although earlier studies with short-term follow-up had failed to demonstrate a significant difference in terms of survival after KT between HCV-positive and HCV-negative patients [97,111,112], with longer follow-up studies, it has been shown that HCV has a negative impact on outcome after KT that becomes evident after 5 years post-KT [97,113,114]. Meta-analyses of observational studies spanning longer follow-up periods showed that the presence of anti-HCV antibody was an independent and significant risk factor for death and graft failure after KT, and cirrhosis and hepatocellular carcinoma were significantly more frequent in HCV-positive KT recipients [115]. Worse outcomes after

KT in HCV-positive patients are associated with a higher incidence of both humoral and chronic rejection [113], a higher frequency of acute glomerulopathy [116] and *de novo* glomerulonephritis [117–119]. A systematic review of 18 observational studies found that the combined hazard ratio in HCV-positive/KT recipients was 1.69-fold (1.33–1.97, $P < 0.0001$) and 1.56 times (1.22–2.004, $P < 0.0001$) greater than that of HCV-negative/KT recipients for mortality and graft loss, respectively [120].

Moreover, a study focusing on evaluation of graft failure after KT in HCV-positive Spanish patients demonstrated that among recipients who were alive and had a conserved graft function 1 year post-transplant, the 4-year graft survival was significantly worse in HCV-positive versus HCV-negative patients (89.5% vs. 94.4%, respectively, $P < 0.005$). Interestingly, acute rejection, a higher degree of proteinuria and decreased renal function, more graft biopsies, and lesions of *de novo* glomerulonephritis, and transplant glomerulopathy were all associated with HCV positivity. Furthermore, serum creatinine and proteinuria 1 year after transplant, acute rejection, HCV positivity and systolic blood pressure were independent risk factors for graft loss. Notably, patient survival was also significantly different in HCV-negative (96.6%) vs. HCV-positive (94.5%, $P < 0.05$) transplant recipients, and serum creatinine and diastolic pressure at 1 year post-transplant, HCV positivity, and recipient age were independent risk factors for death. These authors determined that HCV-associated renal injury occurs precociously with proteinuria, increased serum creatinine associated with chronic allograft nephropathy, transplant glomerulopathy, and less frequently, HCV-associated *de novo* glomerulonephritis [121].

In addition to its direct effects on the liver, HCV infection increases post-transplantation morbidity by increasing the risk for *de novo* or recurrent HCV-associated glomerulopathies [117,119,122,123]. Cryoglobulinemic or noncryoglobulinemic membranoproliferative glomerulonephritis and membranous glomerulonephritis are the most frequent glomerular lesions observed among HCV-positive KT recipients [117,118], and the pathogenesis seems to be in relation to deposition of immune complexes containing viral RNA in the glomerulus [5,124]. Other lesions such as transplant glomerulopathy, anti-cardiolipin-related thrombotic microangiopathy [125], and fibrillary glomerulonephritis [49] have also been described. Recurrence of HCV-associated renal disease may potentially have a negative impact on graft survival and has been associated with higher serum creatinine levels [119,126]. Until now, there is no specific therapy for the treatment of HCV-related glomerular lesions after KT, but rituximab, an anti-CD20 antibody, has been both safe and effective in some cases of HCV-related post-transplant cryoglobulinemia [127].

After KT, immunosuppression may reactivate HCV infection and increase the risk of liver disease progression, which may have a more rapid and aggressive course in this population when compared to immune-competent patients [128]. HCV positivity in KT recipients was associated with an adjusted hazard ratio of death of 2.38 (95% CI, 1.69–3.37), with 5- and 10-year survival rates of 90% and 79%, respectively, for HCV-negative patients, significantly in contrast with the 77% and 50%, respectively, observed in HCV-positive subjects, and higher rates of death due to cardiovascular disease (adjusted HR = 2.74), malignancy

Table 2. Key points on hepatitis C virus (HCV) infection in patients with end-stage renal disease and kidney transplant recipients.

Key points
• Although sanitary measures have reduced the rate of infection with hepatitis C virus in patients with end-stage renal disease and hemodialysis in most developed countries, it is still frequent and constitutes the major cause of liver disease in this population.
• Regular liver function test monitoring and testing for anti-HCV antibodies every 6 months is recommended in hemodialysis patients to screen for the infection, although normal transaminases are frequent and the diminished antibody formation may yield false-negative results.
• Once the infection is detected, assessment of liver function includes periodic biochemical testing, determination of HCV-RNA levels, and ultrasound imaging. Liver biopsy remains the gold standard in selected cases in whom histological information for decision making regarding antiviral treatment. The noninvasive FibroScan test can be used alternatively to establish the presence of fibrosis and safely repeated to evaluate fibrosis progression.
• HCV infection determines reduced survival in patients with end-stage renal disease when compared to their HCV-negative counterparts, even in the absence of direct renal involvement by HCV in the form of glomerulopathy.
• Antiviral treatment must be considered in all patients with end-stage renal disease, although pre-existing anemia may preclude traditional therapeutic schemes using ribavirin or may warrant dose reduction, which may be partly responsible for the low sustained viral response rates observed in this population. New direct antiviral agents in ribavirin-free combinations may improve the tolerability and efficacy of treatment against HCV.
• Notwithstanding the fact that mortality after kidney transplant is increased in HCV-positive recipients, in comparison with the non-HCV population, transplantation still represents a better chance of survival than remaining on hemodialysis.
• In addition to end-stage renal disease, kidney transplant recipients represent a difficult-to-treat population, especially as interferon is associated with acute rejection. Also in this setting, new direct antiviral agents in IFN-free combinations might prove to be valuable treatment strategies, although their efficacy and their safety profiles, especially regarding preservation of renal function and avoidance of graft rejection, still warrant thorough evaluation.

(adjusted HR = 2.52), and hepatic failure (adjusted HR = 22.1) were observed [41].

Anti-HCV treatment after KT with the traditional regimen of peg-IFN and RBV is at present not recommended, due to low SVR rates and graft rejection [129,130], although in cases of acute, fibrosing cholestatic hepatitis, it may be considered [131]. With the advent of new antiviral agents, however, these obstacles may hopefully be hurdled.

Future perspectives

There is a need to clarify several aspects, such as the impact on survival after SVR while still waiting for KT, the increasingly more evident relationship between cardiovascular disease [132] and diabetes in patients with ESRD with HCV infection, and the actual impact of donor HCV positivity in KT HCV-positive recipients, in order to determine whether the apparent negative that has been observed [133] effect is marginal, and actually the major deleterious consequences correspond to the pre-existing HCV infection in the recipient.

More evidence is needed regarding safety and efficacy of new antivirals, especially interferon-free regimens. Trials including difficult-to-treat patients such as those with ESRD and transplant recipients are needed to establish their efficacy and safety in these patients. Although in the case of sofosbuvir, for example, no dose adjustment is needed for cyclosporine nor tacrolimus, although it must be kept in mind that these specific studies were performed on healthy volunteers, and clearly, possible interactions between new antiviral agents and medications used after KT must be carefully and comprehensively evaluated [134]. Finally, new guidelines are compelling in light of new pharmacological approaches to the treatment of HCV, with particular focus on special populations such as those with severe renal impairment and transplant recipients. Table 2 summarizes the key points reviewed regarding HCV infection in ESRD and KT recipients.

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