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REVIEW PAPER

Hepatitis C inflection in dialysis patients: a link to poor clinical outcome?

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Abstract Among the 350,000 maintenance dialysis patients in the USA, the mortality rate is high (20–23% per year) as is the prevalence of hepatitis C virus (HCV) infection (5–15%). An additional same number of dialysis patients in the USA may be infected with HCV but have undetectable HCV antibodies. Almost half of all deaths in dialysis patients, including HCV-infected patients, are due to cardiovascular disease. Since over two-thirds of dialysis patients die within 5 years of initiating dialysis and because markers of malnutrition–inflammation complex syndrome (MICS), rather than traditional cardiovascular risk factors, are among the strongest predictors of early death in these patients, the impact of HCV infection on nutritional status and inflammation may be a main cause of poor survival in this population. Based on data from our cross-sectional and limited longitudinal studies, we hypothesize that HCV infection confounds the association between MICS and clinical outcomes in dialysis patients and, by doing so, leads to higher short-term cardiovascular events and death. Understanding the natural history of HCV and its association with inflammation, nutrition and outcomes in dialysis patients may lead to testing more effective anti-HCV management strategies in this and other similar patient populations, providing benefits not only for HCV infection but the detrimental consequences associated with this infection. In this article, we review the link between the HCV infection and mortality in dialysis patients and compare HCV antibody to molecular methods to detect HCV infection in these individuals.

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Keywords Hepatitis C · Dialysis · Cardiovascular death · Malnutrition–inflammation complex syndrome · Transcription mediated amplification

Introduction

Hepatitis C virus (HCV) infection is currently the most common cause of chronic liver disease in the world [1]. Certain populations, including maintenance dialysis patients, have a significantly higher prevalence of HCV infection, ranging from 5% to 25% or even higher according to the recent literature [2–5]. This population may serve as an exceptional model to study the impact of HCV infection on outcomes, especially because the short-term death risk is extremely high in dialysis patient [6]. In this article, we review the possible link between HCV infection and poor outcome in dialysis patients and compare diagnostic tests used to detect HCV infection in this population.

Poor outcomes of dialysis patients

In the United States, there are currently over 350,000 individuals with end-stage renal disease (ESRD) who are dependant on maintenance hemodialysis treatment (MHD, 92% of all dialysis patients) or chronic peritoneal dialysis (PD, 8% of all dialysis patients) for their survival [6]. According to the estimates of the United States Renal Data System (USRDS), the number of dialysis patients in the USA will approach one-half million or even higher by the year 2010 [6, 7]. The estimated number of dialysis patients in the westernized countries acrosss the globe is approximately 1.5 million with a similar exponetial growth [8]. These patients experience lower quality of life [9], greater morbidity, higher hospitalization rates and increased mortality, currently 23% annually, despite many recent improvements in dialysis treatment and techniques [6, 7, 10].

Approximately two-thirds of all dialysis patients in the USA die within 5 years of initiation of dialysis treatment, a 5-year survival worse than that expected in the majority of patients with malignancies [11]. The causes of death in dialysis patients are diverse; however, approximately half of all dialysis patients die of cardiovascular diseases [6, 7, 10]. Extrapolation of findings from the general population has led to decades of focusing on treating such conventional cardiovascular risk factors in dialysis patients as hypertension, obesity, hypercholesterolemia and hyperhomocysteinemia. However, survival has not improved substantially in the past two decades [12]. Consistent with this notion, cardiovascular outcomes did not improve among dialysis patients who were administered atorvastatin in the 4D trial [13]. Clinical trials using folic acid to correct hyperhomocysteinemia in dialysis patients generally have been negative [14–16]. Additional efforts have targeted other possible correlates of high dialysis mortality such as dialysis dose or dialysis membrane. However, several recent multi-center clinical trials including the HEMO [17] and ADEMEX [18] studies failed to show any survival advantage of increasing dialysis dose in ESRD patients [18]. Hence, there appear to be other prevailing risk factors contributing to this substantial and persistent mortality rate in the dialysis population.

Malnutrition–inflammation–cachexia syndrome

Dialysis patients have a high prevalence of malnutrition (20–60%) and inflammation (15–50%) [19–24], both of which are strongly associated with many nutritional measures and clinical outcomes in the same direction. As yet, the relative contributions of measures of these two conditions to each other and to outcomes in dialysis patients are not well defined; therefore, we have suggested the term ‘‘malnutrition–inflammation complex (or cachexia) syndrome’’ (MICS) to denote the important contribution of both to ESRD outcome [19, 25]. The MICS may be a plausible cause of poor outcomes such as poor quality of life, more frequent hospitalization, refractory anemia and increased mortality [19]. The etiology of malnutrition and inflammation in dialysis patients is not clear, but probable causes are discussed in

publications by our group and others [19, 26–32]. Some of these factors such as reduced food intake due to anorexia can lead to both malnutrition and inflammation and can also be a consequence of MICS [32] (Fig. 1). Hence, the known overlap between malnutrition and inflammation in dialysis patients may have its root at the etiology level.

MICS and atherosclerotic cardiovascular disease

In the general population, indicators of inflammation such as serum C-reactive protein (CRP) level are stronger predictors of cardiovascular events than LDL-hypercholesterolemia [33, 34]. Since inflammation is much more common in CKD patients [20, 35–38], MICS may predispose dialysis patients to atherosclerotic cardiovascular disease at least by virtue of its inflammatory component [39–41]. Dialysis patients with coronary heart disease often have low serum albumin [42, 43] and elevated acute phase reactants [40, 44, 45]. Inflammation might cause direct endothelial dysfunction via stimulation of intercellular adhesion molecules in dialysis patients [46]. However, in the general population, inflammation, similar to traditional cardiovascular risk factors, exerts its deleterious effects on a ''long-term'' basis, whereas the MICS appears to result in poor outcome within a much ''shorter'' period of time. This *temporal discordance* is probably the key element to understanding the problem [36, 37, 47]. Hence, although the association between atherosclerosis and MICS in dialysis patients is well documented, it is not known how or *via* which *temporal* constellations the MICS interacts with traditional risk factors in such unique ways not observed in the general population. Hepatitis C may be an important role-player in this regard (see below).

Prevalence of hepatitis C infection in dialysis patients

Infection with HCV, the most common cause of chronic liver disease in the United States and probably in most other countries [48], is particularly common in the dialysis patient population [2, 49–51]. Since HCV infection is most effectively transmitted by exposure to infected blood, dialysis patients are at relatively high risk for acquiring

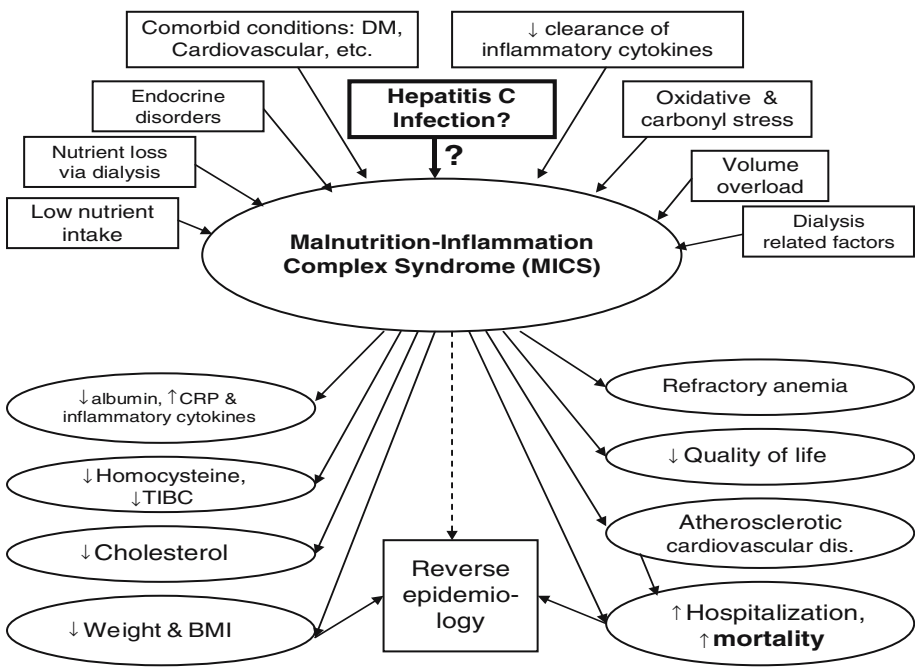

Fig. 1 Possible link between HCV infection and outcome in dialysis patients via the interplay of the MICS

HCV from parenteral exposure during hemodialysis treatment. Although there have been major advances in the control and treatment of HCV in the general population, the incidence and prevalence of HCV infection in the dialysis patient population have not changed significantly in the last decade [2]. In the US dialysis patient population, the incidence of HCV infection has remained approximately 1–3% per year, whereas the prevalence is reported to be approximately 8–15% [2, 50, 51]. However, most data are based on detecting HCV antibody. Hence, the true prevalence of HCV infection in dialysis patients may be even higher (see below).

The striking discrepancy in prevalence of HCV infection between dialysis patients and the general population may not be necessarily related to the renal disease, because some studies have indicated that HCV infection is more common in hemodialysis patients when compared to those who undergo peritoneal dialysis, a renal replacement therapy with less blood exposure [2]. Other studies have indicated increasing prevalence of HCV infection with greater duration of hemodialysis treatment [2, 5] and continuing incidence of new HCV infections in hemodialysis patients (Fig. 2), [52], suggesting that infection control efforts in dialysis centers may be insufficient. Consistent with the latter findings, we have recently showed that dialysis treatment vintage was associated with higher HCV infection prevalence [53]. Although this may be related to more cumulative risk of exposure to infectious sources over time, the possibility of a cohort effect should also be considered i.e., patients whose dialysis treatment started in previous years had higher risk of HCV infection as a result of less stringent HCV infection control measures in the past [2, 5].

Hepatitis C and malnutrition–inflammation complex

Among nutritional conditions, obesity is associated with a poorer outcome in HCV infected patients without CKD [54–56]. However, no clear data is currently available as to whether obesity or body fat affects clinical outcomes in HCV-positive dialysis patients. This is a particularly interesting and clinically relevant question, because obesity is invariably reported to confer survival advantages to dialysis patients, a relationship dubbed the ''reverse epidemiology'' [57–61]. We have found that HCV-infected dialysis patients have a higher prevalence of hypoalbuminemia when compared to non-HCV infected counterparts [51, 62, 63]. Studies on host response to HCV suggest that inflammatory cytokines such as IL-6, IL-1β, and TNF-α have a key role in hepatitis pathogenesis [64–67]. IL-6 and TNF-α levels correlate with the degree of hepatitis activity in HCV infected patients without ESRD [66, 68–70]. Levels of TNF-α and IL-1β are higher in HCV-infected dialysis patients compared to healthy controls, and TNF-α levels correlate with severity of liver disease in HCV-infected adults [68, 70]. Moreover, interferon therapy for HCV attenuates spontaneous production of these inflammatory cytokines. These associations have not yet been well examined in HCV-infected dialysis patients.

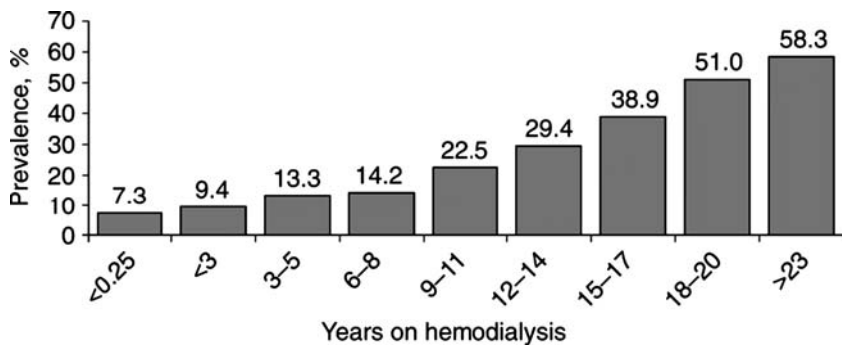

Fig. 2 Association between time on dialysis (vintage) and HCV infection risk in dialysis patients from the Dialysis Outcome Practice Pattern Study (DOPPS) (recreated with permission from Fissell et al. [52])

HCV and mortality in dialysis patients

HCV-infected dialysis patients might develop progressive chronic liver disease with associated long-term morbidity and mortality from cirrhosis [54–56]. However, many dialysis patients may not live long enough to experience these long-term consequences of HCV. Several studies [51, 71–76], including a recent meta-analysis [49], suggest that HCV infection is associated with a significant worsening of patient survival on dialysis (Table 1). Pereira et al. [71] showed that all cause death in HCV-infected dialysis patients was 41% higher than HCV uninfected dialysis patients. Espinoza et al. [72] found that mortality among Spanish dialysis patients who were anti-HCV antibody positive was 12% vs. 9% among those negative for anti-HCV antibody. Stehman-Breen et al. [73] examined 200 dialysis patients for HCV infection using PCR and found that PCR+ patients were at significantly increased risk of death compared to the HCV PCR negative patients. Although a larger study from Japan of 1,470 patients found an association between HCV infection and death [74], no studies have investigated the relationship between HCV infection and death from a population perspective (except for ours [51, 76]), and none have adjusted for markers MICS, which are important and relatively recently identified predictors of mortality [19, 77]. We have studied DaVita national database of dialysis patients across the USA and found, for the first time, that short-term risk of both all-cause and cardiovascular mortality is significantly higher in HCV infected dialysis patients compared to others (Fig. 3) [51, 76]. Nevertheless, others had assumed the excess death in HCV-infected patients would be due to liver disease [71–74].

The true impact of HCV infection on survival and other clinical outcomes in dialysis patients cannot be explained by means of its long-term complications. In other words, the majority of dialysis patients who are infected with HCV may not live long enough to die of long-term HCV complications. This hypothesis, if true, has major clinical implications in our approach to HCV infected dialysis patients. If the main issue is indeed the high rate of short-term mortality in HCV-infected patients [51], it is also expected that short-term effects of HCV infection, rather than its known long-term complications, relate to poor survival. Since MICS is among the most determining predictors of short-term survival in dialysis patients, the interaction between HCV infection and MICS may be a key to understanding the true nature of HCV infection and its confounded course in dialysis patients.

Table 1 Major studies indicating higher death rates among HCV infected dialysis patients

Author & reference	Sample size	Source, cohort length	Death hazard ratio (95% CI)	Comments
Pereira et al. [71]	287 EIA+ & 286 random controls	14 US transplant centers	1.41 (1.01–1.97)	Higher RR of liver disease death (2.39)
Stehman-Breen et al. [73]	220 pts (34 HCV RNA+ pts)	Single center (Seattle), 3 yrs	1.78 (1.01–3.14)	Both EIA and PCR were tested
Nakayama et al. [74]	1,470 pts (19% anti-HCV+ pts)	Multi-center (Japan), 6 yrs	1.57 (1.23–2.00)	Cirrhosis: 5.5% vs. 0 & ca 8.8% vs. 0.4
Kalantar-Zadeh et al. [51]	2,778 (13% or 363 EIA+)	DaVita USA database, 2 yrs	1.41 (1.01–1.97) [< 65 yrs old]	↑ cardiovascular death in HCV+ pts
Kalantar-Zadeh et al. [76]	13,664 (12% or 1,585 EIA+)	DaVita USA database, 3 yrs	1.38 (1.25–154) for all dialysis pts	↑ death risk in all subgroups

EIA: enzyme immuno assay; yrs: years; RR: relative risk; pts: patients

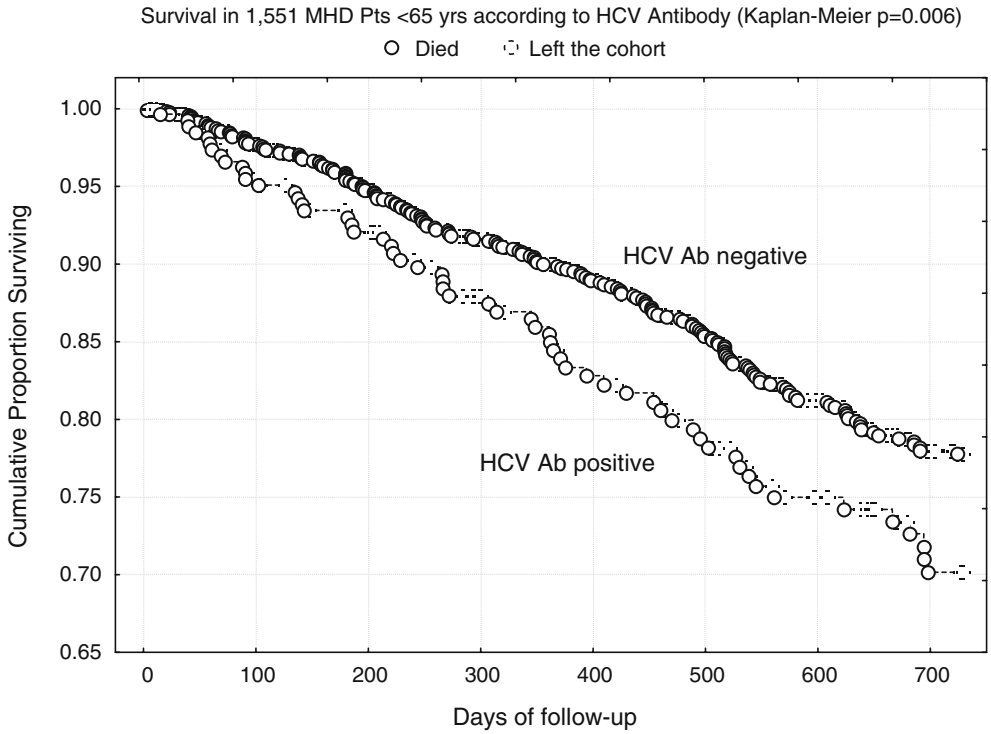

Fig. 3 Kaplan–Meier cumulative proportion of surviving patients according to HCV antibody positivity in 2,778 MHD patients. Upper panel: all age groups, Lower panel: MHD patients younger than 65 years (recreated with permission from Kalantar-Zadeh et al. [82])

HCV diagnostic tests for dialysis patients

Diagnostic tests for HCV infection can be divided into four broad categories (Table 2): (1) Tests of liver function and structure such as liver enzymes and liver biopsy; (2) Serologic assays that detect antibody to HCV or its antigen; and (3) Molecular assays that detect or quantify HCV RNA. Additional HCV tests include HCV viral load and HCV genotyping. Liver function tests such as aminotransferases (AST/SGOT or ALT/SGPT) levels may be only mildly to moderately, if at all, elevated in HCV-infected dialysis patients [2, 50, 78–81]. A newly elevated ALT may be somewhat more specific, but not adequately sensitive, for the detection of chronic HCV infection in this population [2, 80, 81]. However, we have recently showed that the AST, which is routinely and

Table 2 HCV diagnostic tests for dialysis patients

Category	Diagnostic test	Advantages	Disadvantages
Liver tests & structure	Liver enzymes	Ubiquitous tests, low-priced	Non-sensitive, non-specific
	Liver biopsy	High reliability	Invasive, changes in late stage
HCV serology	EIA	Inexpensive, screening tool	Low sensitivity in dialysis pts?
	RIBA	Confirmatory for EIA+	Not more sensitive than EIA
	Core antigen	Non-molecular detection	New test, limited data
HCV molecular (qualitative)	TMA	Highly sensitive	Expensive
	RT-PCR	Highly sensitive	Expensive
HCV molecular (quantitative)	bDNA	Quantitative	Expensive
	RT-PCR	Quantitative	Expensive

EIA: enzyme immuno assay; RIBA: radio immuno blot assay; TMA: transcription mediated amplification; RT-PCR: reverse transcriptase polymerase chain reaction

monthly measured in almost all dialysis clinics in the USA, has clinically relevant sensitivity and specificity profile for HCV infection screening [82].

HCV screening assays

EIA test has many advantages in the diagnostic setting including ease of use, low variability, automation, and low cost [83]. One commonly used screening test is enzyme immuno-assay (EIA), e.g. Abbott HCV EIA 2.0 (Abbott Park, IL), which detects antibodies to recombinant antigens from the core (C22) and non-structural regions 3 (C33) and 4 (C100) of the HCV. However, EIA may have inherent shortcomings in the ESRD population [80, 81, 84, 85]. Dialysis patients with HCV infection may display undetectable HCV antibodies [62]; the false negative status could occur at the late stages of HCV infection because of the compromised immune system or effect of MICS in these patients, resulting in deficient or absent antibody response [70, 86, 87]. Indeed, in other immuno-compromised states such as advanced AIDS, the EIA may fail to detect HCV infection [88]. In a recent study, we found that those dialysis patients who were diabetic and had undergone dialysis for a significantly longer time, were more likely to be EIA–but HCV RNA+, which may indicate the higher likelihood of immune suppression [62].

HCV molecular assays

Molecular-based assays that detect HCV RNA such as PCR [79, 85, 89, 90] and Transcription Mediated Amplification (TMA) [82, 85] are assumed to be the most sensitive diagnostic tests and may pick up additional HCV-infected patients that are EIA negative. Umlauf et al. [91] showed that the PCR method may have inadequate sensitivity to detect HCV infection in dialysis patients with a low viral level or with fluctuating patterns of viremia. PCR assays may also be adversely affected by the presence of heparin, a substance commonly used during hemodialysis and often present in blood samples from dialysis patients [84, 85, 92]. However, the TMA may be more sensitive than the PCR, while maintaining the same high specificity [85]. The TMA is a ultrasensitive HCV RNA qualitative assay that can detect minute amounts HCV RNA [85, 93–98]. Since TMA can detect fewer than 50 HCV copies/ml and less than 6 HCV International Units/ml (World Health Organization, 96/790, Geneva, Switzerland), it may allow early identification of virus replication and thorough verification of viral clearance. The TMA specificity is reported to be 99.6%, which minimizes the risk of false positive results and increases confidence that positive results reflect true viremia.

Several studies have shown the utility of the TMA in detecting HCV infection in the general population [85, 93, 97]. Krajden et al. [97] examined 300 specimens including 112 samples that were indeterminate via EIA but PCR negative, and 79 samples that were EIA positive and PCR negative. Their data suggested that TMA was more sensitive than PCR and had a greater throughput. Comanor et al. [93] examined 97 patients treated for HCV, in whom HCV RNA was not detected by PCR. TMA detected HCV RNA in 27 (34.6%) end-of-therapy (EOT) and 76 (97.4%) follow-up samples from relapsing patients, but not in any of the EOT or follow-up samples from sustained responders. The investigators concluded that the detection of HCV RNA by the TMA-based assay could help redefine EOT response and assist in the antiviral management of HCV infection.

HCV molecular assays in dialysis patients

To our knowledge, there are only three studies [62, 85, 99] in which the TMA was tested in dialysis patients. Khan et al. [85] examined both TMA and PCR in 80 EIA+ and 100 EIA– dialysis patients for kidney transplantation evaluation; 11 EIA+ patients were PCR– but TMA+, whereas only two patients had the opposite discordance. Among EIA– patients, five were TMA+ (including 2 PCR+). Khan et al. concluded that the TMA identified more active HCV infection than PCR and that the PCR was significantly less sensitive in detecting HCV

infection compared to the TMA in dialysis patients [85]. However, their sample represented only those dialysis patients who underwent transplant evaluation. Rigopoulou et al. [99] examined EIA, TMA and HCV genotyping in 366 Greek ESRD patients; 132 patients (36%) were EIA+ or TMA+, including 44 TMA+ alone, 16 EIA+ alone and 72 positive for both assays. More than half of the viremic patients had genotype 3a. None of these cross-sectional studies examined whether discordant TMA+/EIA– patients would develop detectable antibody at some point, and if so, what conditions would determine the rate of HCV antibody sero-conversion.

One possible approach to evaluate dialysis patients for HCV infection is to test periodically (semi-annually to annually) using EIA and an HCV RNA test, i.e., TMA or reverse transcriptase polymerase chain reaction (RT-PCR), in those with high index of suspicion. Patients with double positive (EIA+/RNA+) status, estimated to be 8–12%, [62] should probably undergo additional quantitative testing including viral load measurement and HCV genotyping (Fig. 4). The discordat EIA–/ RNA+ patients, who may represent up to 10% or higher proportion of all dialysis patients and are usually remained undiagnosed, [62] need additional RNA test to exclude false positive RNA results. The discrepant EIA+ but HCV RNA patients may indicate those dialysis patients who have successfully cleared the HCV infection. For the latter patients, the recombinant immunoblot assay (RIBA) can serve as an optional confirmatory test to rule out false positive EIA results (Fig. 4).

Medical treatment and counseling

Currently interferon alpha (IFN-α) in both native and pegylated forms should be considered for HCV infected dialysis patients, especially those who have signs of liver disease (e.g., shown in liver biopsy) or need to undergo kidney transplantation [100]. For example, a regimen of 3 million units of IFN-α thrice weekly for 6–12 months (if tolerated) appears safe and effective [48, 69, 78, 101–106]. Close observation for significant side effects is routine. In dialysis patients, Ribavirin is currently not recommended [107], although several small pilot studies have been examining its safety and efficacy in CKD patients [107–109]. The utility of HCV genotyping as a predictor of response to medical treatment in dialysis patients is not clear, even though in the general population, HCV genotype 1 (out of 6 major HCV genotypes) appears more resistant to IFN-α treatment, some studies in dialysis patients have not shown any

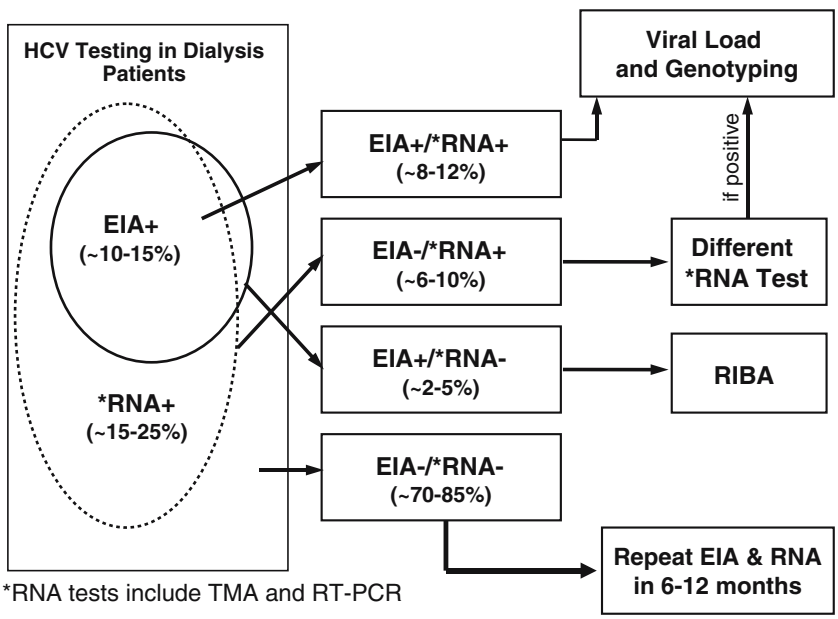

Fig. 4 A possible approach to HCV testing in dialysis patients (EIA: enzyme immuno assay; RIBA: recombinant immuno blot assay; RNA: ribonucleic acid based tests including transcription mediated amplification [TMA] and reverse transcriptase polymerase chain reaction [PCR])

clear association between HCV genotype and response to medical therapy [103].

Many opinion leaders do not recommend treatment of HCV infection in dialysis patients who are not wait-listed for renal transplantation, because the life span of dialysis patients is typically shorter than the time needed for HCV sequalae to occur.

HCV infection control in dialysis patients

According to the Center for Disease Control and Prevention (CDC), HCV positive dialysis patients do not have to be isolated from other patients or dialyzed separately on dedicated machines [110]. Furthermore, they can participate in dialyzer reuse programs [110]. The CDC guidelines state that unlike hepatitis B virus, HCV is not transmitted efficiently through occupational exposures. Thus, reprocessing dialyzers from HCV-positive patients should not place staff members at increased risk for infection [110]. Nevertheless, some nephrologists and some dialysis facilities do exclude reuse for HCV infected patients. If data pertaining to significantly higher mortality risk in HCV infected dialysis patients are verified, a new paradigm may soon emerge with more conservative approaches to the HCV infection in dialysis clinics.

Future steps

The true incidence and prevalence of HCV infection and its link to MICS and survival among dialysis patients is far from clear. Longitudinal studies in large cohorts of dialysis patients are urgently needed to examine the variations of HCV diagnostic tests and the association between HCV and outcomes in these patients. Such studies will lead to results that may have major implications in the management of HCV infection in both dialysis patients and other similar populations. Focused studies are needed to explore the nature and degree of interactions between HCV and MICS as well as to examine the role of genetic characteristics of HCV infected patients or treatment of MICS in modulating the association between HCV and outcomes. New methods to risk-stratify dialysis patients may be proposed as they relate to the combined effect of HCV infection and MICS. Clinical trials can be designed and conducted based on interventions to modulate cytokine production in HCV infection. Associations between nutritional status such as body fat and HCV infection may lead to examining nutritional interventions to target more favorable outcome in HCV infected dialysis patients. Such studies may lead to better understanding of the role of HCV infection not only in dialysis patients, but also in patients with similar chronic disease states such as AIDS or CHF patients who are co-infected with HCV.

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