POSITION PAPERS AND GUIDELINES

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Management of hepatitis C virus infection in patients with chronic kidney disease: position statement of the joint committee of Italian association for the study of the liver (AISF), Italian society of internal medicine (SIMI), Italian society of infectious and tropical disease (SIMIT) and Italian society of nephrology (SIN)

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Abstract

Hepatitis C virus (HCV) infection is now considered a systemic disease due to the occurrence of extra-hepatic manifestations. Among these, the renal involvement is frequent. HCV infection, in fact, is strongly associated with proteinuria and chronic kidney disease (CKD) and negatively affects the prognosis of renal patients. In the last few years, availability of more specific and effective drugs against HCV has dramatically changed the clinical course of this disease. These drugs may provide further advantages in the CKD population as a whole by reducing progression of renal disease, mortality rate and by increasing the survival of graft in renal transplant recipients. The strict pathogenetic and prognostic link between HCV infection and CKD requires an ongoing relationship among the healthcare professionals involved in the treatment of both HCV infection and CKD. Therefore, Scientific Societies involved in the care of this high-risk population in Italy have organized a joint expert panel. The aim of the panel is to produce a position statement that can be used in daily clinical practice for the management of HCV infected patients across the whole spectrum of renal disease, from the conservative phase to renal replacement treatments (dialysis and transplantation). Sharing specific evidence-based expertise of different professional healthcare is the first step to obtain a common ground of knowledge on which to instate a model for multidisciplinary management of this high-risk population. Statements cover seven areas including epidemiology of CKD, HCV-induced glomerular damage, HCV-related renal risk, staging of liver disease in patients with CKD, prevention of transmission of HCV in hemodialysis units, treatment of HCV infection and management of HCV in kidney transplantation.

Keywords HCV infection · Chronic kidney disease · Direct-acting antiviral agents · HCV in renal transplantation

Introduction

Chronic hepatitis C virus (HCV) infection is a leading cause of chronic liver disease and is now considered as a public health concern with a worldwide prevalence rate of 1–2%. HCV infection is associated with an increased morbidity and mortality secondary to hepatic injury and to the associated extrahepatic complications. Among these, kidney involvement is frequent and includes proteinuria, different types of glomerulonephritis, cryoglobulinemia and chronic kidney disease

(CKD). It is now widely accepted that HCV infection predisposes to the onset of CKD; moreover, it worsens the prognosis of renal patients by increasing the risk of ESRD and mortality in non-dialysis CKD patients, mortality rate in hemodialysis patients and loss of graft in kidney transplant recipients.

The knowledge of the HCV genome has permitted the development of new drugs, the so-called direct-acting antiviral agents (DAA) that can achieve much higher sustained virologic response rates than previous therapeutic regimens based on the use of interferon with or without ribavirin. From a renal perspective, these drugs have a double advantage: DAA can improve prognosis of patients with established CKD and, on the other hand, can effectively prevent the occurrence of CKD de novo. This latter point is particularly attractive as a primary preventive strategy aimed at controlling the epidemic growth of CKD worldwide and consequently at reducing the burden of CKD complications and associated costs.

Management of CKD patients with HCV infection obviously requires a multidisciplinary approach in order to appropriately select potential candidates to DAA therapy, identify the better drug combination and manage the occurrence of adverse effect of therapy. On this regard, the main scientific societies involved in the care of this high-risk population in Italy (Italian Association for the Study of the Liver-AISF, Italian Society of Infectious and Tropical Disease-SIMIT, Italian Society of Internal Medicine-SIMI and Italian Society of Nephrology-SIN) have decided to constitute a joint committee to produce the present position statement. Statements cover seven areas including epidemiology of CKD, HCV-induced glomerular damage, HCV-related renal risk, staging of liver disease in patients with CKD, prevention of transmission of HCV in hemodialysis units, treatment of HCV infection and management of HCV in kidney transplantation. This document is not a formal guideline, but is intended as a support in the decision-making process of treatment of HCV infected patients carrying the whole spectrum of renal diseases, from conservative phase to renal replacement therapy (dialysis and transplantation). Therefore, the purpose of this position paper is to discuss some major controversial issues from different perspectives (nephrology, hepatology, infectivology, internal medicine, and gastroenterology) by providing reasoned statements, which can support the management of CKD patients with HCV infection in the daily clinical practice. Sharing specific evidence-based expertise of different healthcare professionals is the first step to obtain a common ground of knowledge in which instate a model for multidisciplinary management of this population.

Epidemiology of chronic kidney disease: classification and prevalence

Statement 1.1   Cause of renal disease, estimated glomerular filtration rate (eGFR) and albuminuria are the three parameters for staging Chronic Kidney Disease (CKD). The same CKD classification, based on alterations of GFR and albuminuria persisting for > 3 months, can be adopted for general population and patients with HCV infection.

Rationale

CKD classification is based on three parameters: the cause of renal disease (glomerular, vascular, tubulointerstitial, cystic or congenital), renal function, and the presence of renal damage [1]. Abnormalities of renal function (estimated by eGFR) and/or renal damage (testified by albuminuria, abnormalities of urinary sediment, altered renal histology demonstrated by renal biopsy, structural damage of kidney evidenced by renal imaging and history of renal transplantation) must persist for at least 3–6 months in order to define "chronic" the renal disease. Renal function is classified in six categories of eGFR and albuminuria in three categories defined as normal (A1), moderate (A2) and severe (A3) (Fig. 1). Albuminuria represents the most important marker of renal damage and the most powerful risk factor for progression of CKD. This means that an albuminuric patient will start dialysis well before than a non-albuminuric patient, even in the presence of similar age, gender, eGFR and comorbidities. Albuminuria can be assessed as daily excretion in 24 h urine collection or on a first morning void urine specimen, as ratio with urinary creatinine (albumin/creatinine ratio, ACR); this can be useful for non-nephrologists because it avoids the need of validating the correctness of 24 h urine collection. Interestingly, urine dipstick can easily detect albuminuria and it can be used as screening strategy; if positive, the dipstick must be confirmed subsequently by quantitative laboratory measurement. Staging of CKD provides crucial information also on the prognosis of CKD patients because global risk including death, cardiovascular (CV) events and end-stage renal disease (ESRD) increases exponentially with eGFR decline and with increase in albuminuria category (Fig. 1) [1].

The ability of residual nephrons to compensate the renal impairment explains why CKD patients are frequently asymptomatic even in more advanced stages of disease. This intrinsic feature of CKD contributes to the scarce

Fig. 1 CKD Classification proposed by KDIGO Guidelines and estimated age-standardized prevalence (%) in Italian general population [2]. Colors refer to global prognosis according to KDIGO Guidelines [1]: green, low risk (in absence of other markers of renal disease, patients do not have CKD); yellow, risk moderately increased; orange, high risk; red, very-high risk. (Color figure online)

		Persistent albuminuria categories		
		A1 (Normal)	A2 (Moderate)	A3 (Severe)
		ACR <30 mg/g 24h Ualb <30 mg/24h 24h Uprot <150 mg/24h Dipstick Negative	ACR 30-300 mg/g 24h Ualb 30-300 mg/24h 24h Uprot 150-500 mg/24h Dipstick Trace to 1+	ACR >300 mg/g 24h Ualb >300 mg/24h 24h Uprot >500 mg/24h Dipstick > 1+
eGFR categories	G1: Normal or high (eGFR≥90 ml/min/ 1.73m2)	68.63	2.35	0.69
	G2 Mildly decreased (eGFR 60-89 ml/min/ 1.73m2)	24.67	1.24	0.29
	G3a: Mildly to moderately decreased (eGFR 45-59 ml/min/ 1.73m2)	1.57	0.29	0.01
	G3b: Moderately to severely decreased (eGFR 30-44 ml/min/ 1.73m2)	0.28	0.11	0.05
	G4: Severely decreased (eGFR 15-29 ml/min/ 1.73m2)	0.04	0.03	0.08
	G5: Kidney failure (eGFR <15 ml/min/ 1.73m2)	0.04	0.00	0.03

eGFR, estimated glomerular filtration rate; ACR, Albumin to creatinine ratio; 24h Ualb, 24 hours urinary albumin excretion; 24h Uprot, 24 hours urinary protein excretion.

awareness of CKD. Indeed, only 10% of patients with CKD had knowledge of their disease [2]. An unacceptably low awareness of CKD (16–17%) has been also detected among physicians [3, 4].

Classification of CKD, based on eGFR and albuminuria, must be implemented also in CKD patients with HCV infection, due to the frequent association between these two diseases. An observational study in 24,642 subjects from general population in Taiwan has documented a prevalence of CKD about three-fold higher in patients with HCV infection with respect to those non-infected (16.5% versus 6.1%) and a prevalence twice of significant proteinuria (11.6% versus 5.0%) [5]. Similar findings were found in 552 patients HCV positive followed in a Gastroenterology clinic as compared with 313 patients without infection matched for age, gender and race (9.6% versus 5.1%) [6]. The association between HCV infection and CKD is constantly growing in last years [7]. The most important caveat for CKD patients with HCV infection is related to the eGFR estimation in those who have cirrhosis. Indeed, cirrhotic patients have several underlying conditions (decreased creatinine production secondary to decreased hepatic creatine synthesis and conversion to creatinine, increased tubular creatinine secretion, and muscle wasting) that contribute to falsely low serum creatinine concentrations leading to overestimation of GFR. This is particularly true for Jaffé assay of creatinine, which is influenced by "non-creatinine" chromogens present in the plasma (typically bilirubin) more than enzymatic assay [8]. Therefore, as direct methods for GFR measurement (inulin clearance and other direct methods using injected exogenous radiolabeled substances) are impracticable in clinical practice, nephrologists and gastroenterologists need to be aware that creatinine measurements overestimate renal function in patients with cirrhosis, and what may appear to be relatively small increases represent much larger changes in eGFR. As such, creatinine results should be interpreted cautiously in cirrhotic patients taking into account age, sex, degree of liver impairment and muscle mass. This aspect has two important clinical consequences: first, creatinine is included in the model for end-stage liver disease (MELD) score used for liver transplant allocation and, second, the selection of DAA regimen and monitoring of renal function during treatment is usually based on creatinine-based eGFR estimates.

Statement 1.2   The prevalence of CKD in the Italian general population is about 7%.

Rationale

Previous studies reported estimates of CKD in general population varying from 6.4 to 12.7% [9] likely due to the heterogeneity of study design, such as differences in population sampling, age, extent of geographic area, equation used to estimate eGFR and examined stages. The cardiovascular risk profile in Renal patients of the Health Examination Survey (CARHES) study has provided more accurate data by showing that the crude prevalence of CKD (95% confidence interval) was 7.05% (6.48–7.65) in Italian general population. Early stages constituted 59% of the CKD patients [Stage G1–2 A2–3: 4.16% (3.71–4.61) and Stage G3–5: 2.89% (2.51–3.26)]. CKD prevalence slightly decreased after age standardization to the resident population (overall: 6.7%) (Fig. 1) [2]. We can therefore estimate that, in Italy, there is a total number of 2.180.542 adult persons (age 35–79 years) with CKD (49.3% males), most with early disease (60.4%) and older age (69.8%). An ACR of ≥ 30 mg/g was detected in 4.77% of subjects. In particular, ACR was moderate (ACR 30–300 mg/g, formerly defined as microalbuminuria) in 84.3% of albuminuric persons, with the remaining 15.7% having severe albuminuria (ACR > 300 mg/g, formerly defined as macroalbuminuria). At multivariate regression analysis, age, obesity, hypertension, diabetes, CV disease and smoking were all independent correlates of CKD [2].

CKD has a lower prevalence in Italy, in particular for advanced stages, when compared with similar national surveys outside Europe (13.1% in US, 12.5% in Canada, 11.5%

in Australia) [9]. This occurs despite older age and unfavorable CV risk profile of the whole population. Therefore, it has been hypothesized that features inherent to the population living in Italy may be protective for CKD development, even in the presence of negative risk profile. Whether this is a 'renal' aspect of the genetic low background risk [10], and/or dependent on the still high adherence to the Mediterranean diet [11, 12], deserves further studies.

Statement 1.3   People with CKD must be considered at increased risk for mortality, cardiovascular disease, progression to advanced CKD and hospitalization.

Rationale

CKD population is exposed to a high risk of morbidity and mortality due to several metabolic and hormonal dysfunctions and hydro-electrolyte abnormalities that negatively affect prognosis. Indeed, besides traditional risk factors common to the general population, renal patients experience several CKD-dependent complications (such as hypertension, anemia, secondary hyperparathyroidism, oxidative stress, and malnutrition among others) that increase exponentially the renal and CV risk of this population thus explaining why CKD is now considered a *"disease equivalent"* of diabetes mellitus [13, 14]. Staging CKD by eGFR and albuminuria is of paramount importance to optimize risk stratification in this population (Fig. 1).

Prognosis of CKD patients in Italy has been evaluated by the TArget Blood pressure LEvel (TABLE) cohort study in 1248 patients with CKD stage 3–5 (GFR < 60 mL/min/1.73 m^2), steadily followed from 2003 to 2010 in 25 Nephrology clinics in Italy [15–17]. Risk factors more frequently recorded in such population were hypertension (88%), dyslipidemia (58%), proteinuria (52%) and anemia (27%) [15]. TABLE study evidenced an incidence of ESRD of 8.3 per 100 patients-year (95% CI 7.4–9.2) and of all-cause death of 5.9 per 100 patients-year (95% CI 5.2–6.6) [16]. Besides age, history of CV disease, anemia and hyperphosphatemia, proteinuria was the most powerful risk factor predicting progression of renal disease in patients with eGFR 15–60 mL/min/1.73 m^2 while in the more advanced stage (eGFR < 15 mL/min/1.73 m^2) proteinuria was not associated with the risk of ESRD [16]. Adverse outcomes associated with proteinuria were evident in both younger and older patients (> 75 years) [17]. The cause of renal disease also plays an important prognostic role [18]. Indeed, patients with diabetic nephropathy or autosomal polycystic kidney disease as primary renal disease have a risk of ESRD two- and five-fold higher, respectively; this holds true independently from the achievement of optimal control of those risk factors (proteinuria, hypertension and anemia) that

induce a faster decline of renal function [18]. Several observational studies have reported a strong association between pre-existing CKD and the risk of hospitalization. Cardiac disease, hypertension and infection were the most frequent primary causes of hospitalizations whereas progression of CKD and acute kidney failure were the most common secondary cause of hospitalization [19]. Go et al. reported an independent, graded association between GFR and the risk of hospitalization in 1,120,295 adults within a large, integrated system of health-care delivery with at least one creatinine measurement between 1996 and 2000 [20]. Indeed, age-standardized incidence rate of hospitalizations increased exponentially from 13.5 per 100 person-year in subjects with eGFR > 60 mL/min/1.73 m^2 to 144.6 per 100 person-year in patients with eGFR < 15 mL/min/1.73 m^2; after multiple adjustments, hospitalization risk increased from 14% in stage G3a, up to 315% in stage G5 [20]. In addition, CKD patients were also more exposed to the risk for hospitalization with infections [21], longer hospital stay and higher risk of readmission [22].

Statement 1.4   Patients with HCV infection are more predisposed to develop Acute Kidney Injury.

Rationale

Severity of acute kidney injury (AKI) can be graded in three stages based on the entity of creatinine increase and urinary output. AKI grade 1 is characterized by a creatinine increase between 50 and 100% of baseline value or by an absolute increase ≥ 0.3 mg/dL associated with oliguria (diuresis < 0.5 L in 12 h). In the grade 2, creatinine increases 2–3 times the baseline level and oliguria persists for > 12 h; finally, AKI grade 3 is classified by either a serum creatinine 3 times higher than baseline, or an increase to ≥ 4.0 mg/dL or initiation of renal replacement therapy and anuria for more than 12 h [23].

As previously described for CKD, albuminuria plays a major role also for stratifying the risk of AKI. Indeed, a meta-analysis of 13 studies involving about 1.3 millions of patients, has evidenced that the risk of AKI progressively increased not only with eGFR decline (from 1.6 when eGFR is 60–74 up to 10.7 when eGFR < 15 mL/min/1.73 m^2) but also in the presence of increasing albuminuria (from 1.6 when ACR is 10–29 mg/g up to 4.0 when ACR is > 300 mg/g) [24]. For each eGFR category, the implementation of ACR improves risk stratification. As an example, a non-diabetic patient with eGFR in the range 45–59 mL/min/1.73 m^2 has a risk of developing AKI varying from 2.72 in the absence of albuminuria up to 7.4 and 14.1 in the presence of moderate and severely increased albuminuria, respectively [24].

Patients with HCV infection are more prone to develop AKI represented by either a renal functional involvement or acute tubular necrosis. In a retrospective analysis of the US Nationwide Inpatient Sample of the Healthcare Cost and Utilization Project, 4,603,718 adult hospitalizations with an associated HCV diagnosis from 2004 to 2012 in the US were identified. The proportion of HCV positive hospitalizations complicated by dialysis-requiring AKI increased significantly from 0.86% in 2004 to 1.28% in 2012 [25]. In HCV infected patients, the presence of CKD was associated with an adjusted risk for AKI requiring dialysis (OR 2.17, 95% CI 2.03–2.33) similar to that observed for chronic liver disease (OR 2.11) and greater than that associated with heart failure (OR 1.79), hypertension (OR 1.78) or diabetes (OR 1.10) [25]. In-hospital mortality was significantly higher in hospitalizations complicated by dialysis-requiring AKI versus those without (27.38% vs. 2.95%; adjusted odds ratio 2.09, 95% CI 1.74–2.51). The most important limitation of the study was the use of administrative data (ICD-9-CM codes) to define HCV infection.

In some studies in HIV infected populations [26, 27], the association between HCV co-infection and AKI remained significant in multivariate analysis. The pooled relative risk of AKI in patients with HIV-HCV co-infection was 64% higher than in those without HCV co-infection without significant heterogeneity [28]. However, another study in a cohort of HCV infected patients (n = 267), reported that HIV co-infection was related with AKI whereas HCV genotype and HCV viral load did not [29].

It is important to keep in mind that patients experiencing an AKI episode not only were more prone to develop CKD or dialysis but they had a two-fold greater risk of mortality [30]. Even more suggestive were the data provided by Bucaloiu et al. [31]. In that study, 1610 patients with reversible AKI that resolved within 90 days after discharge were matched, using a propensity-score across multiple parameters, with 3652 control patients who had not experienced AKI [31]. Reversible AKI was associated with an 18% higher risk of death, and, more importantly, with a greater risk of de novo CKD (HR 1.91, 95% CI 1.75, 2.09). This occurs likely because of the presence of renal fibrosis or tubulointerstitial injury induced by the AKI episode that in the long-term promotes chronicity of renal damage. Thus, a resolved episode of hospital-associated AKI has important implications for the longitudinal surveillance of patients without preexisting, clinically evident renal disease. This concept applies to all categories of at-risk patients without preexisting CKD, including those with HCV infection, in which management strategies for primary CKD prevention become mandatory.

Statement 1.5 Timing of referral of CKD patients to nephrologist should be based on eGFR, albuminuria and complications.

Rationale

The above-mentioned low CKD awareness translated in an insufficient referral to nephrology clinics even for patients with advanced CKD (only 55% of patients with GFR < 30 mL/min/1.73 m^2 were referred to nephrologists) [4]. This low referral rate is associated with a greater risk of death and ESRD in comparison with patients regularly followed in nephrology clinics [32]. Furthermore, delayed referral to nephrologists associated with higher mortality, increased risk of hospitalization, longer hospital stay, impaired metabolic status, worse anemia control and healthcare expenditures [22, 32–34].

Referral to nephrologists should be recommended when eGFR is below 30 mL/min/1.73 m^2 independently from albuminuria level or in patients with severe albuminuria (category A3) independently from eGFR category [1]. However, earlier nephrology referral is indicated in the presence of CKD-specific complications (Table 1).

Table 1 Clinical and laboratory conditions requiring nephrology referral

GFR < 30 ml/min/1.73 m^2 (GFR categories G4-G5) independently from albuminuria level

Severe Albuminuria[a], independently from eGFR

Rapid eGFR decline (> 5 mL/min/year or change of GFR category with at least 25% GFR reduction)

Hematuria

Resistant hypertension (defined as BP above target despite the use of ≥ 3 drugs including a diuretic)

Severe anemia (hemoglobin < 11 g/dL)

Electrolyte disturbances

Hyperphosphatemia

Secondary hyperparathyroidism

Hereditary kidney disease

[a]Defined as either ACR > 300 mg/g or 24 h albuminuria > 300 mg/day or 24 h proteinuria > 500 mg/day or Dipstick > 1

HCV infection and glomerular damage: pathogenetic-laboratory data and histopathological aspects

Statement 2.1   All patients with glomerular disease (especially those with cryoglobulinemic nephritis) should be screened for HCV infection.

Rationale

HCV infection is associated with a large spectrum of glomerular diseases and their clinical sequelae (Table 2). The most frequently observed is the cryoglobulinemic glomerulonephritis (cryoglobulinemic nephropathy) secondary to type II mixed cryoglobulinemia (MC), and histologically characterized by Type 1 membranoproliferative glomerulonephritis (MPGN) [35, 36].

Other nephropathies, including MPGN without cryoglobulinemia, membranous nephropathy (MN) and mesangio-proliferative glomerulonephritis, are rarely associated and only occasional observations exist describing focal segmental glomerulosclerosis, fibrillary or immunotactoid glomerulopathies or thrombotic microangiopathy in HCV infected patients [37].

Statement 2.2   The pathogenetic mechanisms may be related indirectly and directly to the viral infection. The risk of measures leading to a rapid increase of viral replication and the consequent increase of viremia should be taken into account.

Rationale

The pathogenesis of HCV-related nephropathy has not yet been fully clarified, but several piece of evidence suggests the intervention of different mechanisms, either directly related to kidney infection or mediated by the host's immune response. From this point of view, the kidney appears to have peculiar characteristics that make the study of HCV-related damage of special interest and potential translational value.

The role played by mechanisms secondary to the immune reaction of the host have been especially emphasized [38, 39]. Above all, the latter appears to be represented by the effect of the production and deposition of circulating (more or less cryoprecipitating) immune complexes.

Nevertheless, the role played by the direct infection of cells (renal and/or lymphatic) has also been shown. In the MC, a combination of direct and indirect effects of the viral infection on the B-cell compartment leads to the clonal expansion of B cells producing RF (B RF cells), and the

Table 2 Main HCV-Associated Kidney Diseases, clinical manifestations and suggested pathogenetic factors

Kidney disease	Clinical manifestations	Hypothetical pathogenetic factors
Cryoglobulinemic MPGN	Nephritic syndrome, nephrotic syndrome	Cryoglobulin deposition in glomerular capillaries, mesangium, and urinary space; mesangial deposits of immune complexes including HCV antigens, Ig and complement
Non-cryoglobulinemic MPGN	Nephritic syndrome, nephrotic syndrome	Mesangial deposits of immune complexes (HCV antigens, Ig, and complement components)
MN	Nephrotic syndrome	Subepithelial deposits of immune complexes (HCV antigens, Ig, and complement components)
IgA nephropathy	Isolated proteinuria and/or hematuria	Mesangial deposits of immune complexes (HCV antigens, Ig, and complements components)
Focal segmental glomerulosclerosis	Nephrotic syndrome, Isolated proteinuria	Direct injury by HCV on podocytes of epithelial cells
Immunotactoid glomerulopathy/ fibrillary glomerulonephritis	Nephrotic syndrome, Isolated proteinuria and/ or hematuria	Mesangial and capillary wall deposition of immune complexes (HCV antigens, Ig, and complement components)
Mesangial proliferative glomerulonephritis	Isolated proteinuria and/or hematuria	Direct effect of HCV on mesangium by TLR-3 or MMP-2
Tubulointerstitial nephritis	Proteinuria	HCV deposition in tubular epithelial and infiltrating cells (direct cytotoxicity and/or immune-mediated injury)
Thrombotic microangiopathy	Nephrotic syndrome, Isolated proteinuria and/ or hematuria	Endothelial injury by direct activity of HCV

MPGN membranoproliferative glomerulonephritis, *MN* membanous nephropathy, *Ig* immunoglobulin, *TLR-3* toll-like receptor 3, *MMP-2* matrix metalloprotease 2

production of cryoglobulins, that exert pathogenetic effects on the kidney [35].

Therefore, the kidney appears to be an ideal model for expressing the HCV extrahepatic pathogenicity. In fact, its microstructure is suitable to examine the HCV-associated molecules, like cryoglobulins or other circulating immune complexes, antigens and antibodies. At the same time, it has been shown that the renal parenchyma expresses the main factors implicated in the various phases of HCV infection, such as LDL receptors, glycosaminoglycans, CD81 SR-B1 receptors and TLR-3 [39]. In addition, it cannot be excluded that the virus enters the renal parenchyma also via a "Trojan Horse" mechanism, using either infected B cells [40] and/or exosomes [41]. Finally, kidney cells would be equipped with the cellular machinery required for replication. Concerning available data, HCV RNA has been found in mesangial cells, tubular epithelial cells, and endothelial cells of glomerular and tubular capillaries, and HCV-related protein deposits have been found in the mesangium [42, 43]. However, due to the technical difficulties in the evaluation of HCV viral infection in *in vivo* tissue samples (as a result of the rather high sensitivity of detection methods and the possible contamination by circulating particles), further studies are needed to better ascertain these data.

Special attention should be paid to cryoglobulinemic nephropathy. It is known that MC is a systemic vasculitis whose pathogenetic mechanisms are at the same time based on a lymphoproliferative disorder (remote pathogenesis) and circulating immune complexes (cryoglobulins) [44]. The systemic vasculitis resulting from this condition involves mainly small-sized arteries and veins and essentially derives from the deposition of immune complexes composed of RF, IgG, HCV RNA and complement on the endothelial surface. The histopathologic analysis in the case of cryoglobulinemic glomerulonephritis (see below) shows that cryoglobulins are deposited in the glomerular capillaries and mesangium. Furthermore, there are usually histologic signs of vasculitis and downstream fibrinoid necrosis [39]. The nephrotoxicity of cryoglobulins deposited in the kidney is suggested to be secondary to affinity of IgM-RF for cellular fibronectin in the mesangial matrix [38, 45]. Cryoglobulins may also induce endothelitis via anti-endothelial activity and complement activation leading to the increased expression of VCAM-1 and platelet aggregation [39].

Toll-like receptors (TLRs) may also have a role in HCV-associated renal injury. Interestingly, the glomerular expression of TLR4 (which is constitutively expressed by podocytes) and fibronectin was found to be upregulated in a murine model of cryoglobulinemic glomerulonephritis [46], and TLR3 expression was increased in mesangial cells of HCV-related MPGN patients [47].

The direct mechanisms of kidney damage may occur as a consequence of the active infection of cells and/or through the mere attachment of the virus to cell surface receptors, possibly inducing several direct cytopathic effects, that can be extrapolated in the kidney as endothelitis, mesangial inflammation and podocyte injury. The contribution of these more direct effects is supported by several observations. These include the fact that over 50% of the renal lesions occur in the absence of cryoglobulinemia, and a variable proportion without histological evidence of immune-mediated injury. This is particularly evident in the immunocompromised patient, like the patient undergoing organ transplantation (see below). In agreement with the hypothesis of direct pathogenic mechanisms, it has been reported a correlation between levels of viral replication (as indicated by HCV viremia) and damage severity [48]. Despite the above-cited technical limits, some studies have shown HCV replication in the renal tubules in patients with HCV-associated interstitial nephritis [49]. Furthermore, electron microscopic detection of viral like particles has been reported in renal biopsies, performed on HCV-infected patients [50, 51]. HCV-related virus-like particles were about 30–45 nm in diameter and located in electron-dense deposits in the paramesangial areas [51].

Statement 2.3   Testing serum cryoglobulins, complement and RF levels is useful for a correct diagnostic approach, even in patients without symptoms of cryoglobulinemic vasculitis.

Rationale

In the cryoglobulinemic nephropathy, renal biopsy typically shows a pattern of Type I MPGN and it is mostly associated with type II MC [52, 53] (see before). Cryoglobulinemic nephropathy is characterized by the duplication of the glomerular basement membrane (GBM), GBM interposition by mesangial cells (especially monocytes), mesangial proliferation with leukocyte exudation, endoluminal hyaline pseudo-thrombi (corresponding to cryoglobulin precipitates) and rarely extra-capillary proliferation. Immunofluorescence microscopy may reveal C3, IgM and IgG depositions on the capillary wall and mesangium. Intraluminal and subendothelial deposits may have a fibrillary pattern on electron microscopy likely representing cryoglobulin deposition [54]. In addition, one-third of these patients may have vasculitis in the small renal arteries [35, 55, 56]. The laboratory shows typical markers of CM, with FR positivity, consumption of C4 component complement, with, obviously, positivity for HCV markers and positive cryocrit. Given the fluctuations in the cryocrit value and the difficulty of proper sampling, it is recommended to repeat the determination of cryoglobulins after a negative result using stringent conditions [57].

Interestingly, in a large autopsy study, the glomerular deposition of immune complexes was found also in patients without symptomatic glomerulonephritis [58].

If MPGN is the glomerular disorder most strongly associated with chronic HCV infection, several cases of MN have been described in HCV infected patients [53, 59, 60]. The histological findings as well as the clinical presentation of HCV-associated MN are similar to the idiopathic form. Usually, serum complement levels are normal and cryoglobulins and RF are absent in the serum. There are several reports about the association between HCV and FSGS [61, 62] and IgA nephropathy [63–65].

Fibrillary-immunotactoid glomerulopathies may be associated with systemic disorders such as lymphoproliferative disorders, adenocarcinomas, connective tissue diseases and infectious diseases [66]. Six cases of fibrillary immunotactoid glomerulopathies associated with HCV infection have been described [67, 68]. Fibrillary and immunotactoid glomerulopathies are characterized by extracellular deposits of microfibrils within the mesangium and glomerular capillary walls, which do not stain for Congo red [69]. Furthermore, immunofluorescence microscopy reveals IgG, especially IgG4, and C3 in the lesions [66]. On electron microscopy, fibrils with diameters of 16–28 nm and 33–45 nm were observed in fibrillary glomerulonephritis and immunotactoid glomerulopathy, respectively [70].

Statement 2.4   After kidney transplantation in HCV+ patients, the most frequent HCV-associated nephropathy is MPGN (typically associated with cryoglobulinemia, hypocomplementemia and/or RF).

Rationale

HCV-related glomerulopathy represents one of the most frequently reported HCV-associated adverse events after kidney transplantation [71–74]. MPGN was found to be the most common glomerulopathy (5–54% of cases) [75].

In a cohort of HCV-infected renal transplant recipients ($n = 50$), a greater rate of non-treated controls developed chronic allograft nephropathy compared with IFN-treated patients, 41% (13/32) *vs.* 6% (1/18), $P = 0.009$. According to a logistic regression analysis, the absence of antiviral therapy before renal transplant was a risk factor for chronic allograft nephropathy with an odds ratio of 12 ($P = 0.02$) [76].

Renal diseases occurring in HCV-infected patients after kidney transplantation include also MN, minimal change disease, renal thrombotic microangiopathy, FSGS, and acute and transplant glomerulopathies [75, 77]. Cryoglobulinemia, hypocomplementemia or RF were typically absent.

Hepatitis C virus infection and renal risk: acquisition and progression of chronic kidney disease

Statement 3.1   All patients who receive diagnosis of CKD should be screened for HCV infection.

Rationale

Testing for HCV appears logical in patients with CKD as several pieces of evidence support the notion that chronic HCV infection plays a role in the development of CKD. Prevalence and incidence rates of hepatitis C are more frequent in patients with CKD (particularly, in those undergoing regular hemodialysis) than among those with normal kidney function [78]. Although controversial data exist [79], several observational studies have suggested that HCV favors the incidence or progression of CKD in the general population. A meta-analysis of observational studies ($n = 9$ longitudinal studies; 1,947,034 unique patients) demonstrated a relationship between positive anti-HCV serologic status and the incidence of CKD in the adult general population that was 43% higher (HR 1.43, 95% CI 1.23–1.63) [80]. Significant heterogeneity was noted and this precluded more definitive conclusions. Based on current evidence, patients with HCV infection should be regarded as being at greater risk of CKD, regardless of the presence of conventional risk factors for kidney disease.

Statement 3.2   Screening for HCV infection should be made with enzyme immunoassay followed by nucleic acid testing. Non-dialysis CKD patients should be screened at the time of referral in outpatient clinic.

Rationale

Infection with HCV is characterized by increased serum levels of alanine aminotransferase (ALT) in general population. However, blood testing for ALT has weak diagnostic value in renal patients, because in both maintenance hemodialysis and non-dialysis CKD, ALT levels most commonly fall within the lower limit of normal range [81, 82]. The exact cause of this phenomenon is unclear and various agents have been cited: vitamin B6 deficiency, uremic toxins accumulation and malnutrition. Detection of antibodies against HCV (anti-HCV) by the 4th-generation enzyme immunoassay (EIA) is the most commonly used screening tool for HCV infection [83]. Third-generation EIAs have high sensitivity (98.8%) and specificity (100%) [84, 85]. However, the time

between HCV infection and the appearance of detectable antibodies (serological window period) is generally more than 40 days using third generation EIAs [86]. In 2008, the 4th-generation EIA has become available, which allows to detect the HCV antibody significantly earlier than the other assays [83]. A proportion of dialysis patients might test negative for anti-HCV, but test positive for persistence of viral particles (HCV-RNA) in the serum [87]. In fact, immune-compromised patients might either exhibit a delay in antibody production or an absence of specific antibodies following acute HCV infection. Dialysis units with a high prevalence of HCV infection were estimated to have an 18% false-negative of anti-HCV test [87]. The Kidney Disease Improving Global Outcome (KDIGO) HCV Work Group had already recommended that all CKD patients be tested for HCV [88]; we suggest that in hemodialysis units initial testing by immunoassay should be considered; if positive, immunoassay must be followed by nucleic acid testing (NAT). Some issues such as frequent unavailability of test kits, costs, and limited reproducibility hamper NAT testing. Recently, 2018 EASL recommended HCV core antigen detection and quantification by means of EIA when HCV RNA tests are not available and/or not affordable, as an alternative tool for early diagnosis of HCV infection [89].

Statement 3.3 All patients who receive diagnosis of HCV infection should be screened for kidney disease by using urinalysis and eGFR. If the initial screening for CKD is negative, patients with diagnosis of HCV infection and detectable HCV RNA should be tested for CKD on a regular basis (i.e., twice a year).

Rationale

CKD and HCV infection are connected in different ways [90, 91]; HCV infection and CKD are prevalent in the general population of developed countries, patients on regular hemodialysis are at risk of acquisition of HCV and some types of kidney disease are precipitated by HCV infection. On the other hand, conventional risk factors for CKD such as aging, diabetes mellitus, arterial hypertension, and metabolic syndrome do not fully explain the current frequency of CKD in the adult general population of developed world. Cohort studies performed either in patients with diabetes [92], or with biopsy-proven primary glomerulonephritis [93], or with HIV and HCV co-infection [28] have confirmed a significant association between anti-HCV positive serologic status and development of CKD. In a pooled analysis of longitudinal studies (n = 8, with 105,462 unique patients) positive anti-HCV serologic status was associated with an increased risk of low eGFR among HIV-infected patients.

The summary estimate for adjusted hazard ratio was 1.64 (95% CI, 1.28–2.0, P < 0.001) in HIV-HCV co-infected patients compared with those having HIV mono-infection. No between-studies heterogeneity was found (P value by Q test = 0.08) [94].

The predictive role of HCV viral load on CKD has been evidenced recently in 13,805 Taiwanese participants, enrolled in the Risk Elevation of Viral Load Elevation and Associated Liver Disease/Cancer in HCV (REVEAL-HCV) Study Group [95]. Compared to non-HCV-infected participants, the probability of having CKD in patients with chronic HCV infection significantly increased linearly across tertiles of HCV RNA (from 21 to 244% from lowest to higher tertile).

Of note, antiviral therapy for HCV consistently improves hepatic and extra-hepatic outcomes in the adult general population. Among liver transplant recipients with HCV who underwent antiviral therapy for HCV, sustained virologic response (SVR) led to improved eGFR in HCV-infected liver transplant patients with mild CKD before treatment [96]. Some studies, addressing the impact of interferon-based regimens on the development of CKD in the general population, concluded that treatment of HCV might improve renal survival *per se* [6, 97–101]. The Taiwan National Health Insurance Research Database investigated the incidence of ESRD in 12,384 HCV-infected patients receiving antiviral therapy (pegylated interferon plus ribavirin) matched 1:2 with 24,768 untreated patients over a follow-up of 3.3 ± 2.5 and 3.2 ± 2.4 years, respectively. The calculated 8-year cumulative incidence of ESRD accounting for death as a competing event, was 0.15% and 1.32% in treated and untreated patients, respectively (P < 0.001) [99]. Multivariate-adjusted Cox regression revealed that antiviral treatment was associated with lower risks of ESRD (HR, 0.15; 95% CI: 0.07–0.31; P < 0.001) [99].

Statement 3.4 Patients with CKD and HCV infection should be evaluated with serial measurements of eGFR and albuminuria over time to assess the progression of CKD.

Rationale

Besides cryoglobulinemic MPGN, HCV-infected individuals may also be at risk for kidney injury related to decompensated cirrhosis, injection drug use, and concomitant HIV or HBV co-infection. Interestingly, recent evidences suggest that HCV supports the development of atherosclerosis in various tissues and organs including kidneys. HCV can promote atherogenesis through several direct and indirect biological mechanisms including arterial inflammation, insulin resistance, liver steatosis, oxidative stress, hyperhomocysteinemia, and greater production of tumor necrosis

factor-alpha [102–104]. All this findings support a close monitoring of renal damage over time (mainly by eGFR and albuminuria) in order to detect patients with earlier and faster progression of renal disease. Of note, a large observational cohort study involving more than one million of veterans, has evidenced that patients with positive to HCV (10% of cohort) had a doubled risk of starting dialysis and a 22% higher probability of having a faster progression of renal disease (GFR loss > 5 mL/min/year) [105].

Staging of liver disease in patients with chronic kidney disease

Statement 4.1   Liver biopsy should be considered only when clinically needed. A transjugular approach (instead of percutaneous transthoracic route) should be considered in selected circumstances.

Rationale

Although widely performed and established in diagnosing hepatic fibrosis, liver biopsy is an invasive technique with associated morbidity. The most common type of liver biopsy is a percutaneous liver biopsy; however, transvenous liver biopsy (transjugular or transfemoral route) is an alternative technique usually choiced in the presence of ascites, severe coagulopathy or thrombocytopenia contraindicating a percutaneous approach. Transjugular liver biopsy is also adopted when additional diagnostic data is needed (i.e., diagnosis of portal hypertension). CKD patients, and in particular ESRD individuals, frequently have significant hemostatic disorders and hemorrhagic complications, posing additional risks for patients undergoing invasive procedures [106]. Even with a normal INR and platelet count, percutaneous liver biopsy is not entirely safe due to platelet dysfunction associated with uremia. Recent evidence supports the pre-biopsy subcutaneous administration of desmopressin acetate (0,3 μg/kg) in CKD patients with serum creatinine $\geq$ 1.5 mg/dL (and/or eGFR $\leq$ 60 mL/min per 1.73 m^2) as it decreases the risk of bleeding and hematoma size in patients undergoing percutaneous kidney biopsy [107]. Transjugular liver biopsy has been evaluated in the ESRD population and although it is safe, is not widely available and provides smaller samples than the intercostal route.

Statement 4.2   Non-invasive assessment of fibrosis stage by transient elastometry, AST to Platelet Ratio Index (APRI) and Fibrosis 4 (FIB-4) score has been validated in patients with end stage renal disease. In patients with renal disease Fibrotest® is not an accurate predictor of fibrosis stage.

Rationale

Stage of liver fibrosis can be reliably predicted in ESRD HCV-infected subjects by simple and widely available blood tests such as AST levels and platelet count as a part of APRI or FIB-4 scores and have been validated in this population [108]. Transient elastometry (TE) is widely accepted as a reliable non invasive tool to assess the stage of liver disease in patients without renal disease. It has been confirmed that TE was superior to APRI in assessing the severity of hepatic fibrosis and can substantially decrease the need of staging liver biopsy in hemodialysis patients with chronic hepatitis C [109]. Fibrotest® and Actitest® which have been validated as a non-invasive test for assessment of fibrosis and disease activity does not seem to be a reliable non-invasive marker in hemodialysis patients with HCV infection. This is probably due to alteration of apolipoprotein A-1 synthesis in uremia and alpha-2 macroglobulin and haptoglobin alteration by acute phase reaction induced by the dialysis procedure [110].

Statement 4.3   Patients with liver stiffness measurement > 9.2 KPa and/or with APRI > 0.8 and or with FIB-4 > 3.25 should undergo semiannually screening for HCC by US and monitoring of liver function. Prognosis of liver disease in patients with advanced renal disease showing ascites as the only symptom of portal hypertension should be assessed also by measurement of Hepatic Venous Pressure Gradient.

Rationale

Liver stiffness FIB-4 and APRI cut offs with the best accuracy for the diagnosis of cirrhosis have been identified in patients with ESRD in a cross sectional study: they are respectively 9.2 kPa 0,8 and 3,25. Thus, screening for HCC and hepatic decompensation is mandatory in patients showing transient elastometry and/or APRI or FIB-4 scores equal or below these values [109]. Ascites occurrence in patients with ESRD might be related to extrahepatic causes and probably occurs earlier in the course of liver disease in patients with advanced renal disease. Thus in patients where ascites is the only sign of liver decompensation, prognosis should be better assessed by Hepatic Venous Pressure Gradient evaluation [111].

Preventing transmission of hepatitis C virus infection in hemodialysis units

Statement 5.1   Infection control practices should include standard precautions and other patient-care procedures aimed at preventing transfer of blood (or fluids contaminated with blood) between patients, either directly or via contaminated equipment or surfaces. Infection control procedures within dialysis units should be reviewed on a regular basis with observational audits.

Rationale

The prevalence of HCV infection is still higher in patients undergoing maintenance dialysis than in the general population (Table 3) [112–119]. Introduction of screening of blood (and blood products) for HCV and reduction in blood transfusion requirements following introduction of erythropoiesis-stimulating agent therapy has virtually eliminated the occurrence of post-transfusion HCV infection among patients on dialysis. Nosocomial transmission is currently the most likely source when hemodialysis patients develop anti-HCV antibody. Its occurrence has been highlighted by several epidemiological findings, such as the relationship between frequency of HCV infection and time spent on dialysis treatment, higher prevalence of HCV in hemodialysis than peritoneal dialysis or home hemodialysis, and the highly variable prevalence of HCV from unit to unit [120].

Transmission of HCV occurs easily through parenteral route and its control is therefore a challenge in dialysis units. The occurrence of nosocomial transmission of HCV

Table 3 Prevalence of anti-HCV antibody positive serologic status among patients on maintenance hemodialysis (high- and low-income countries)

Author [reference]	Prevalence of anti-HCV antibody	Country	Year
Alashek W [111]	31.1% (2382/7659)	Libya	2012
Garcia-Agudo [112]	5.6% (708/12,472)	Spain	2013
Goodkin [113]	3.3% (85/2575)	UK	2013
Goodkin [113]	8.6% (1766/20,534)	US	2013
Goodkin [113]	16% (413/2581)	Italy	2013
Goodkin [113]	16.8% (1278/7607)	Japan	2013
Ummate [114]	15% (15/100)	Nigeria	2014
Lioussfi [115]	59.7% (40/67)	Morocco	2014
Vidales-Braz [116]	18.2% (58/318)	Brazil	2015
Duong [117]	7% (8/113)	Vietnam	2015
Malhotra [118]	33.5% (88/262)	India	2016

in hemodialysis units has been confirmed using molecular virology by various authors who identified clusters of closely related isolates of HCV by means of phylogenetic analysis, both in studies of individual units with high seroconversion rates and in multicenter studies. Parts of the HCV genome (especially hypervariable region 1) are highly variable and lend themselves to fingerprinting of each isolate or quasi-species using nucleic acid sequencing [88].

The most likely source of HCV transmission between patients treated in the same dialysis unit is cross-contamination from supplies and surfaces (including gloves) because of failure to follow infection-control procedures within the unit. Transmission via the internal pathways of the dialysis machine has been cited in a few circumstances. Other possible transmission routes are direct contact between the patients, common infected blood donor, invasive procedures outside the unit with contaminated material used for both the source and the newly infected patient, and holiday dialysis in developing countries.

Some systematic reviews have analyzed the mechanisms of nosocomial transmission of HCV within dialysis facilities [88, 120, 121]. The conclusion was that the identification of the sources of de novo HCV infection is difficult due to several reasons, such as the asymptomatic nature of HCV infection, the long latency period of HCV infection, the lack of details in the dialysis treatment records, and the retrospective nature of the investigations addressing the sources of HCV spread within dialysis units. In addition, patients on maintenance dialysis undergo multiple treatments per week- this hinders the identification of source patients in dialysis outbreaks. A systematic review of 36 studies using molecular virology to address outbreaks of HCV infection within hemodialysis units provided evidence of nosocomial transmission of HCV within hemodialysis units [120].

Infection control procedures against transmission of blood-borne pathogens (including HCV) include Standard Precautions and other patient-care procedures which have been recommended for all hemodialysis patients since 1977 [122]. Standard precautions are adopted in all inpatient hospital settings, and include use of gloves, gowns, or masks whenever needed to reduce the risk of transmission of blood-borne and other pathogens from both recognized and unrecognized sources. Other precautions are unique to the hemodialysis setting and have been reiterated by the Centers for Disease Control and Prevention (CDC) in 2001 [123] and later [124], regardless of the patient's serological status (Table 4).

There are no RCTs evaluating the impact of regular audits on transmission of HCV infection within dialysis units. Some observational studies reported that implementing regular audits as part of quality improvement programs results in lowered rates of bloodstream infections [125]. However, the goal of these audits was the control of bloodstream

Table 4 Relevant infection control practices for control of HCV within dialysis units

Universal (Standard) precautions
Infection control procedures unique to the hemodialysis setting
No supplies, instruments, or medications should be shared between patients
Clear separation between clean and contaminated areas
Cleaning and disinfection of non-disposable items, environmental surfaces, and dialysis machines between uses
Screening for HCV
Anti-HCV testing (should be repeated semi-annually), ALT testing (should be repeated monthly) for susceptible patients
Infection control training and education
Regular audits to ensure improved adherence to recommended practice

infections and access-related bloodstream infections instead of HCV infection alone. An audit from nine dialysis units in Spain reported that health workers used gloves on 92.9% of occasions, hands were washed only in 35.6% of the time after patient contact, and only in 13.8% of the time before patient contact [126]. The degree of compliance to hand washing practices was evaluated by direct observation of hemodialysis staff at work. Poor adherence to hand washing was associated with the number of shifts per hemodialysis unit per day and with higher patient-to-nurse ratios. Compliance to infection control procedures was greater in the acute than chronic hemodialysis facilities [125]. Whether or not higher hand hygiene standards promoted by regular audits translates in a lower incidence of HCV between hemodialysis patients needs to be clarified.

A big drop in prevalence and incidence rates of HCV infection within hemodialysis units has been observed after the routine implementation of infection control practices and the use of sensitive serological assays. A large survey from Belgium revealed a decrease in the prevalence of positive anti-HCV serologic status from 13.5% in 1991 to 6.8% in 2000 [127]. The prevalence rates reported in Table 3 are lower in comparison with those noted in 1990s [120]. However, nosocomial transmission of HCV within hemodialysis units is still a health concern all over the world [128–130]. As an example, a large number of cases of acute HCV infection have been notified to the CDC between 2014 and 2015- about 36 patients with de novo HCV infection in 19 different hemodialysis clinics from eight US states [131]. According to this evidence, the CDC have again highlighted the importance of implementation and adherence to recommended control practices in dialysis settings [132]. The role of patient-care practices in the spread of HCV between patients on hemodialysis has been emphasized recently. Indeed, most epidemiological surveys had collected such information by self-reports assessing the extent to which some practice-care procedures were conducted. Shimokura et al. gathered data on patient-care practices by direct observation and reported a relationship between the prevalence of HCV and specific patient-care practices after adjusting for

non-dialysis related HCV factors [133]. Reusing priming receptacles without disinfection (Odds ratio, 2.3, 95% CI, 1.4–3.9), handling blood specimens in contaminated areas (OR, 2.2, 95% CI, 1.3–3.8), and using mobile carts to deliver intravenous medications (OR, 1.7; 95% CI; 1.0-2.8) were associated with greater prevalence of anti-HCV antibody [134].

Statement 5.2   Isolation of hemodialysis patients with HCV infection is not suggested.

Rationale

Benefits and arms of isolation for what concerns in-center HCV diffusion remain unclear as robust RCTs are missing [134]. Isolation strategies were those including a number of policies with various grades of intensity, such as using dedicated dialysis machines, staff, room or dialysis shift. Only one RCT has been retrieved and concluded that no difference was found in terms of incidence of HCV infection when comparing the use of dedicated hemodialysis machines for HCV infected patients with the use of non-dedicated machines [135]. The quality of the evidence provided in this RCT was defined very low. Two multicenter, prospective, observational studies (the DOPPS and the Italian study, respectively) both concluded that isolation does not confer protection against transmission of HCV between patients on regular hemodialysis [136, 137]. A prospective observational study from Belgium was able to observe a reduction in the annual incidence of HCV seroconversion from 1.4 to 0% after the reinforcement of universal and hemodialysis-specific practices, without any isolation measures [138]. Identical results have been reported in a single-center trial from Italy [139].

Convincing arguments against the isolation of HCV-infected patients on maintenance hemodialysis exist. The infectivity of HCV is lower than that of HBV, related at least in part to a lower viral load and lack of viability of HCV at room temperature. The adoption of an isolation strategy to prevent transmission of HCV includes the possibility of an

increased risk of HCV infection with more than one genotype. The clinical impact related to infection by various strains of HCV remains to be evaluated. Current tests for detecting HCV based on antibody screening become positive after a serologically silent window (seroconversion time) which can last up to 1 year. Isolating patients on regular hemodialysis on the basis of HBV and HCV serologic status would generate 4 separate cohorts with organizational difficulties and high costs.

In summary, the isolation of HCV-infected dialysis patients is not recommended for preventing transmission of HCV within dialysis units. However, a local isolation policy for HCV-infected dialysis patients should be considered in dialysis units where nosocomial transmission of HCV continues to occur despite reinforcement and audit of infection control procedures designed to prevent transmission of blood-borne pathogens, including HCV. In any case, isolation should not be considered an alternative to the implementation and adherence to the practices recommended in dialysis units.

Statement 5.3 Dedicated dialysis machines for hemodialysis patients with HCV are not recommended.

Rationale

Data regarding the contamination of the ultrafiltrate or dialysate during hemodialysis sessions or peritoneal dialysis by anti-HCV positive patients are controversial [140]. From a theoretical point of view, we cannot exclude passage of virions through the dialyzer membrane of an infected patient with migration from the drain tubing to the fresh dialysate circuit theoretically allowing the virus to pass through the dialyzer membrane to infect another patient; however, the occurrence of back-filtration in the second hemodialysis session is needed. Such a theoretical process seems unlikely in single-pass dialysis machines. Sharing contaminated hemodialysis machines was cited in some reports but the great majority of the studies addressing this topic have excluded transmission of HCV by internal contamination of dialysis machine. External contamination of hemodialysis machines is considered an important modality of transmission of HCV within hemodialysis; an incomplete disinfection of external machine surfaces and other surfaces at the station is a frequent finding in many outbreak reports [120].

Statement 5.4 Chronic hemodialysis patients should be screened for anti-HCV antibody at admission or re-admission to the dialysis center. Susceptible hemodialysis patients should be tested for HCV antibody twice a year. Screening should be anticipated in case of

signs or symptoms of liver disease (ie liver enzymes elevation) and/or in case of occurrence of HCV infection in another patient the same dialysis center.

Rationale

Anti-HCV screening is essential for identifying outbreaks of HCV within hemodialysis units; in fact, HCV infection in dialysis patients is usually asymptomatic but routine serological tests performed serially over time are able to detect serologic conversion and appearance of anti-HCV antibody. The identification of an outbreak of HCV infection among hemodialysis patients should immediately promote an action including the assessment of adherence to standard and dialysis-specific infection control procedures; proper screening of hemodialysis patients susceptible to HCV should be established. In the majority of cases, serologic conversion for anti-HCV antibody in a patient on regular hemodialysis is related to the dialysis environment and this should require to conduct a thorough root cause analysis of the infection and address infection control lapses.

The blood for HCV-RNA or HCV Ag testing should be drawn prior to a hemodialysis session, because the intradialytic reduction of HCV RNA titers during the hemodialysis procedure [141] and the presence of heparin in the blood could lead to a false-negative PCR result. The intradialytic reduction of HCV RNA during the session could explain why the HCV viral load in the dialysis population is not high and does not increase over time despite the immune compromise conferred from uremia [142]. Adsorption of HCV onto dialysis membrane, HCV escape into spent dialysate, destruction of HCV particles or increased interferon (IFN) activity during the dialysis session represent the main mechanisms explaining the reduction of HCV RNA during hemodialysis. A gradual return to pre-dialysis levels within 48 h has been also found [142].

We recommend repeat screening of hemodialysis patients who are not infected with HCV (anti-HCV antibody negative) twice a year, in order to detect new infections by HCV. Hemodialysis patients with risky sexual intercourses should be screened more frequently. In addition, patients who are anti-HCV antibody positive/HCV RNA negative (patients with resolved HCV infection) require periodic screening (twice a year) as they remain at risk for re-infection if exposed. The identification of new infection could represent transmission of HCV within the dialysis center.

When a new HCV infection is identified in a hemodialysis unit, all NAT negative patients within the dialysis unit should be tested for HCV infection and the frequency of subsequent HCV testing be increased. HCV testing should be performed with NAT techniques.

CDC recommends that all maintenance hemodialysis patients be screened for ALT level upon admission and ALT testing be repeated monthly for susceptible patients. Serum ALT levels fall frequently in the range of normal values; however, the majority of hemodialysis patients with de novo HCV infection have higher aminotransferase values [143]. If an unexplained elevation of ALT occurs, the patient should be tested for HCV infection. The exact predictive value of ALT screening for detecting HCV infection is unclear [144]. Due to the asymptomatic course of HCV infection among patients on maintenance dialysis, ALT levels have been frequently used retrospectively to define the likely exposure period for patients who acquired infection.

Treatment of chronic hepatitis C virus in CKD patients

Statement 6.1   Combination of different classes of directly acting antivirals, by acting on different sites of the HCV replication cycle, is essential to obtain a sustained virological response.

Rationale

Treatment of HCV is based on DAAs, i.e., drugs targeting the virus replication cycle [145, 146]. These drugs target key steps of HCV replication: the polyprotein cleavage by the NS3 Protease (Protease inhibitors, PIs), the HCV RNA strain synthesis (NS5B Polymerase inhibitors, of two sorts, nucleoside analogues (NA) and non-nucleosides) and the stabilization of the replication complex and viral release (NS5A inhibitors) [89, 147]. Combination of different classes of DAA is essential to obtain a sustained virological response defined as HCV RNA undetectability 12 weeks after the end of therapy (SVR 12). Although SVR 12 rates in the 90–95% range are now achievable in most patient populations, patients with CKD still represent a group of patients, which requires expert management mainly because kidney function affects the Pharmacokinetics of Sofosbuvir, an NS5B NA that represents a key backbone of several DAA combination regimens.

DAA combinations are essential to maximize SVR rates. Currently two DAA combination strategies can be described:

1. The Sofosbuvir based regimens, which include

   (a) the combination of Sofosbuvir plus a PI (Simeprevir),
   (b) the combination of Sofosbuvir plus an NS5A inhibitor (Velpatasvir, Ledipasvir, Daclatasvir)

   (c) the combination of Sofosbuvir plus a PI and an NS5A (Velpatasvir/Voxilaprevir)

2. The non-Sofosbuvir based regimens, which include

   (a) the combination of a PI plus an NS5A and a non-nucleoside NS5B inhibitor (Ritonavir boosted Pariptarevir/Ombitasvir + Dasabuvir)
   (b) the combination of a PI and an NS5A inhibitor (Grazoprevir/Elbasvir and Glecaprevir/Pibrentasvir)

In this paper we will not analyze all available DAA regimens [89, 148], but rather concentrate only on DAA regimens currently reimbursed by the Italian National Health System, thus excluding the combinations of Sofosbuvir + Simeprevir, Sofosbuvir + Daclatasvir, Sofosbuvir/Ledipasvir and Sofosbuvir/Velpatasvir/Voxilaprevir.

Although, some of these regimens are pangenotypic, which means they are active against all six HCV strains, most of them are restricted in activity to specific genotypes (Table 5).

In this paper we will concentrate only on DAA regimens currently reimbursed by the Italian National Health System, thus excluding the combinations of Sofosbuvir + Simeprevir, Sofosbuvir + Daclatsvir, Sofosbuvir/Ledipasvir and Sofosbuvir/Velpatasvir/Voxilaprevir.

Statement 6.2   The presence of CKD influences DAA Pharmacokinetics.

Rationale

Sofosbuvir (SOF)

Sofosbuvir should be administered at the dose of 400 mg (one tablet) once per day, with or without food. Approximately 80% of sofosbuvir is renally excreted, whereas 15% is excreted in faeces. The majority of the sofosbuvir dose recovered in urine is the dephosphorylation-derived nucleoside metabolite GS-331007 (78%), while 3.5% is recovered as sofosbuvir [89]. Renal clearance is the major elimination pathway for GS-331007 with a large part actively secreted. Thus, currently, no sofosbuvir dose recommendation can be given for patients with severe renal impairment (eGFR < 30 mL/min/1.73 m^2) or with end-stage renal disease due to higher exposures (up to 20-fold) of GS-331007.

Velpatasvir (VEL)

Velpatasvir is metabolised in vitro by CYP2B6, CYP2C8 and CYP3A4. However, due to the slow turnover, the vast majority of drug in plasma is the parent drug. Importantly,

Table 5 DAA regimens for HCV patients according to genotype

Combination regimen	Genotype 1	Genotype 2	Genotype 3	Genotype 4	Genotype 5–6
SOF/LDV ± RBV	Yes	No	No	Yes	Yes
SOF/VEL[a] ± RBV	Yes	Yes	Yes	Yes	Yes
PrOD[a] ± RBV	Yes	No	No	No	No
PrO[a] ± RBV	No	No	No	Yes	No
EBR/GZR[a] ± RBV	Yes	No	No	Yes	No
SOF + DCV ± RBV	Yes	Yes	Yes	Yes	Yes
SOF + SIM ± RBV	Suboptimal	No	No	Yes	No
GLE + PIB[a]	Yes	Yes	Yes	Yes	Yes
SOF + VEL + VOX[b]	Yes	Yes	Yes	Yes	Yes

SOF sofosbuvir, *LDV* ledipasvir, *RBV* ribavirin, *VEL* velpatasvir, *PrOD* paritaprevir / ritonavir / ombitasvir + dasabuvir, *EBR* Elbasvir, *GZR* grazoprevir, *DCV* daclatasvir, *SIM* simeprevir, *GLE* glecaprevir, *PIB* pibrentasvir, *VOX* voxilaprevir

[a]Indicates regimens reimbursed by Italian NHS

[b]Reimbursed only in DAA failures

velpatasvir is transported by P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) and, to a limited extent, by organic anion transporting polypeptide 1B1 (OATP1B1). Biliary excretion of the parent drug is the major route of elimination. The pharmacokinetics of velpatasvir was studied in HCV-negative patients with severe renal impairment (eGFR < 30 mL/min/1.73 m^2). Relative to subjects with normal renal function, velpatasvir AUC was 50% higher and this was not considered to be clinically relevant [89].

Ritonavir boosted Paritaprevir/Ombitasvir ± Dasabuvir (PrOD or PrO)

Paritaprevir is an NS3-4A protease inhibitor, which is metabolised primarily by CYP3A4 and it is given with a low dose of the CYP3A inhibitor ritonavir as a pharmacokinetic enhancer. Ombitasvir is an NS5A inhibitor given in a fixed-dose combination with paritaprevir/ritonavir. The recommended dose of this combination is two tablets of ritonavir/paritaprevir/ombitasvir (50 mg/75 mg/12.5 mg per tablet) taken orally once daily with food. Dasabuvir is a non-nucleoside inhibitor of HCV RNA-dependent RNA polymerase in 250 mg tablets administered twice daily in combination with ritonavir/paritaprevir/ombitasvir in genotype 1 patients. Paritaprevir is excreted predominantly into the feces. Ombitasvir shows linear kinetics and it is predominantly eliminated in the feces. Dasabuvir is metabolized in the liver, and its predominant metabolite is mainly cleared via biliary excretion and fecal elimination with minimal renal clearance [89].

The AUC of paritaprevir was increased 45% in patients with severe renal impairment (creatinine clearance 15–29 mL/min), that of ritonavir 114%, and dasabuvir 50%.

Currently, no dose adjustment is required for patients with mild, moderate or severe renal impairment.

Grazoprevir/Elbasvir (GZR/EBR)

Grazoprevir and elbasvir are available in a two-drug fixed-dose combination containing 100 mg of grazoprevir and 50 mg of elbasvir in a single tablet. The recommended dose of the combination is one tablet taken orally once daily with or without food. Grazoprevir and elbasvir are partially metabolized by CYP3A4, but no circulating metabolites are detected in plasma. The principal route of elimination is biliary and faecal with less than 1% recovered in urine. Grazoprevir is transported by P-gp and OATP1B1, while elbasvir is a substrate for P-gp.

No dose adjustment is required in patients with mild, moderate of severe renal impairment (including patients on hemodialysis or peritoneal dialysis). There is an increase in elbasvir (65%) and grazoprevir (86%) exposure in non-HCV infected subjects with an eGFR < 30 ml/min/1.73 m^2, but this is not considered to be clinically significant [89].

Glecaprevir/Pibrentasvir (GLE/PIB)

Glecaprevir is a pangenotypic PI and Pibrentasvir is a pangenotypic NS5A inhibitor, Glecaprevir/Pibrentasvir should be given at dosing of 300 mg/120 mg (three 100 mg/40 mg tablets), taken orally, once daily with food. Glecaprevir and pibrentasvir are weak inhibitors of cytochrome P450 (CYP) 3A and uridine glucuronosyltransferase (UGT) 1A1 in vivo.

Glecaprevir and pibrentasvir AUC were increased ≤ 56% in non-HCV infected subjects with mild, moderate, severe, or end-stage renal impairment not on dialysis compared to subjects with normal renal function. Glecaprevir and

pibrentasvir AUC were similar with and without dialysis (≤ 18% difference) in dialysis-dependent non-HCV infected subjects. In population pharmacokinetic analysis of HCV-infected subjects, 86% higher glecaprevir and 54% higher pibrentasvir AUC were observed for subjects with end stage renal disease, with or without dialysis, compared to subjects with normal renal function. Larger increases may be expected when unbound concentration is considered.

Overall, the changes in exposures of glecaprevir and pibrentasvir in HCV-infected subjects with renal impairment with or without dialysis were not clinically significant. No dose adjustment of glecaprevir and pibrentasvir is required in patients with any degree of renal impairment including patients on dialysis [149].

Statement 6.3   In HCV patients with CKD stage 4–5 or on hemodialysis, non-Sofosbuvir based regimens should be preferred whenever possible.

Rationale

As previously discussed sofosbuvir is renally eliminated, in patients with mild to moderate renal impairment (eGFR ≥ 30 mL/min/1.73 m^2), no dose adjustments are necessary for the combination of sofosbuvir and velpatasvir. In patients with CKD stage 4 with severely reduced renal function (eGFR 15–29 mL/min/1.73 m^2) or those with CKD stage 5 (eGFR < 15 mL/min/1.73 m^2 or on dialysis) there is a lack of properly conducted trials on sofosbuvir based regimens. Concerns have been raised because of the substantially higher concentrations of sofosbuvir and, most importantly, of its renally excreted metabolite GS-331007 (+ 171% and + 451% AUC_{0-inf}, respectively, as compared with patients without renal impairment). The appropriate

therapeutic dose of sofosbuvir in patients with advanced or end-stage renal disease is not established. For this reason, in HCV patients with CKD stage 4–5 sofosbuvir-free regimens should be preferred whenever possible [89]. No dose adjustment is required in CKD patients when treated with paritaprevir/ombitasvir/dasabuvir, grazoprevir/elbasvir or glecaprevir/pibrentasvir. These regimens were investigated in ad-hoc clinical trials designed to assess the safety and the efficacy in CKD stage 4–5. In the Ruby-1 trials 20 HCV-1 patients without cirrhosis with stage 4 or stage 5 CKD received 12 weeks of paritaprevir/ombitasvir/dasabuvir, the 13 patients infected with genotype 1a received ribavirin 200 mg once daily. The SVR12 rate was 90% (18/20) [150].

In the C-SURFER trial, 122 patients infected with HCV genotype 1 with CKD stage 4 or 5 received grazoprevir and elbasvir for 12 weeks without ribavirin. The SVR12 rate was 94% (115/122), with only one virological failure. The frequencies of renal system adverse events were generally comparable between treatment groups [151]. In the Expedition-4 Trial 104 HCV patients with CKD stage 4–5 of any genotype received 12 week of Glecaprevir/Pibrentasvir the sustained virologic response rate was 98% (102 of 104 patients; 95% confidence interval, 95 to 100). No patients had virologic failure during treatment, and no patients had a virologic relapse after the end of treatment [152].

Statement 6.4   In HCV patients with CKD, Ribavirin free schedules should be preferred.

Rationale

Table 6 shows the optimal duration and schedules of paritaprevir/ombitasvir/dasabuvir, grazoprevir/elbasvir or glecaprevir/pibrentasvir in HCV patients with CKD stage 4–5. Although no direct comparison of these regimens

Table 6 Optimal duration and schedules of DAA regimens for HCV patients with CKD stage 4–5

Combination regimen	Genotype 1a	Genotype 1b	Genotype 2	Genotype 3	Genotype 4	Genotype 5–6
PrOD ± RBV	12–24[a] weeks + RBV	12 weeks	No	No	No	No
PrO ± RBV	No	No	No	No	12 weeks + RBV	No
GZR/EBR ± RBV	12–16 weeks[b] ± RBV	12 weeks	No	No	12–16 weeks[b] ± RBV	No
GLE/PIB	8–12[c] weeks	8–12[c] weeks	8–12[c] weeks	8–16[c,d] weeks	8–12[c] weeks	8–12[c] wks

Paritaprevir/ombitasvir/dasabuvir (PrOD), grazoprevir/elbasvir (GZR/EBR) or glecaprevir/pibrentasvir (GLE in HCV patients with CKD stage 4–5)

PrOD paritaprevir/ritonavir/ombitasvir/dasabuvir, *GZR/EBR* grazoprevir/elbasvir, *GLE/PIB* glecaprevir/pibrentasvir

[a]24 weeks in patients with Child-Turcotte-Pugh class A cirrhosis

[b]16 weeks in patients with HCV RNA > 800.000 IU/mL or NS5A RAS

[c]12 weeks in patients with Child-Turcotte-Pugh class A cirrhosis

[d]16 weeks in patients with a previous failure to PegIFN or SOF

exists, ribavirin-free schedules should be preferred due to accumulation of ribavirin in the blood of patients with kidney impairment leading to increased rates on anemia and treatment related side effects [153]. In addition, the removal of ribavirin by the hemodialysis procedure is poor. If ribavirin has to be used, individualized ribavirin dosing of 200 mg/day or 200 mg/every other day or 200 mg thrice weekly after hemodialysis is recommended, and substantial hematopoietic support is essential [89].

Clinical trials and real-life data clearly showed that also in patients with CKD therapeutic regimens based on DAA are safe and without significant side effects, even if patients treated with ribavirin and/or patients with advanced liver and/or kidney disease should be carefully followed.

Statement 6.5   In certain conditions, sofosbuvir-based regimens and ribavirin can be considered but risk–benefit ratio must be carefully weighed.

Rationale

There are conditions such as in Child-Pugh-Turcotte class B-C patients or those with significant drug–drug interactions in whom paritaprevir/ombitasvir/dasabuvir, grazoprevir/elbasvir or glecaprevir/pibrentasvir are unsafe or contraindicated. In these cases, the combination of sofosbuvir/velpatasvir for 12 weeks $\pm$ Ribavirin can be considered. Ribavirin should be given in HCV-3 infected patients with cirrhosis or in those without cirrhosis who have failed a previous IFN course [89]. The data on sofosbuvir based regimens in CKD patients are scanty and mostly derive from small cohort studies, which included heterogeneous groups of patients with different etiologies of kidney diseases and various degrees of liver disease staging [154, 155]. Consistently across all cohorts, the efficacy of sofosbuvir-based regimens is not reduced by the presence of CKD; however, conflicting results exist in terms of safety signals. In the TARGET 2.0 real-world cohort study, progressive deterioration of renal function and renal symptoms were reported in patients with severe renal impairment receiving a sofosbuvir-based regimen, while others, including a recent meta-analysis, have not confirmed this finding [154–156]. Thus if treatment is urgent and no sofosbuvir-free regimen is available, the risks versus the benefit of sofosbuvir-based regimens should be carefully weighed. Close monitoring is required and treatment should be rapidly interrupted if the kidney damage worsens, as testified by either sudden renal function decline or onset/worsening of albuminuria [89].

HCV and kidney transplantation

Statement 7.1   The prevalence of HCV infection in kidney transplant recipients (KTRs) is high. Kidney transplant is the better therapeutic strategy for patients with ESRD and HCV infection. However, HCV infected KTRs have worse clinical outcome than non-infected.

Rationale

The prevalence of HCV infection in kidney transplant recipients is high with an estimated a prevalence of patients HCV positive of 6.8% [157].

Kidney transplantation is reportedly the better treatment for ESRD patients with HCV infection. A meta-analysis that evaluated nine controlled studies selected from the 378 available on the topic, showed better survival in HCV infected patients undergone kidney transplantation as compared to those who remained on the waiting list [158].

CV disease remains the first cause of death in HCV patients still on dialysis, whereas both CV and infectious diseases accounted for mortality in the group of transplanted patients. It is conceivable that restored kidney function with improved clearance of uremic toxins, together with reduced inflammatory status and oxidative stress may have contributed to the better survival rate of transplanted patients [159]. Furthermore, regression of left ventricular hypertrophy, reported after successful kidney transplantation, may play a role in the decreased CV mortality [160].

However, general transplant outcome of HCV patients is worse than that of non-infected KTRs mainly due to elevated cardiovascular morbidity, increased incidence of post-transplant diabetes and infectious diseases, and to liver disease progression, including cirrhosis and hepatocellular carcinoma [161, 162]. A recent analysis based on the long-term outcome of 33,357 KTRs, found that, among 1470 HCV positive KTRs, HCV was associated with higher risk of death and graft failure. Infection, liver failure and recurrent disease were more common causes of death in HCV positive KTRs than in HCV negative [163, 164].

Although post-transplant immunosuppressive therapy has a permissive effect on liver fibrosis progression through interference with HCV-driven inflammatory milieu, clinical data has shown reduced progression or even partial reversal of liver fibrosis in HCV infected patients after kidney transplantation as compared to those who remained in the waiting list [161].

Last, de novo disease of kidney graft related to HCV infection, and greater occurrence of transplant

glomerulopathy may contribute to the poorer outcome observed in KTRs with HCV infection [164].

Statement 7.2 DAA therapy is effective and safe in HCV infected kidney transplant recipients. Treatment schedule and duration should be performed according available guidelines taking account of liver fibrosis stage, HCV genotype, renal function and drug interactions.

Rationale

Traditional anti-viral therapy with IFN and ribavirin in renal patients was burdened by low SVR (about 35%) and elevated dropout ratio [165]. Remarkably, the immuno-stimulating property of this cytokine was associated with significantly higher rates of acute rejection and worsening of kidney graft function in more than 50% of patients treated with IFN. Thus, the panel of KDIGO released a warning about the adoption of such a therapy after kidney grafting [88] and viral eradication had been generally suggested in dialysis patients waiting for a kidney transplant [166].

By contrast, new available DAA proved to be as effective as safe in KTRs; sustained virological eradication is reported in 90–100% of cases, with low ratio of significant adverse events, while graft function remained stable during treatment in most studies [154, 167–175]. Table 7 presents data on the available studies with DAA in KTRs.

A sofosbuvir-based anti-viral therapy was used in most studies. Colombo et al. conducted an open-label clinical trial and evaluated the safety and efficacy of the daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) in 114 genotype 1–4 kidney transplant recipients with median eGFR ranging from 50 to 60 mL/min [172]. Overall SVR12 was 100% and safety profile was good. A slight eGFR reduction was reported (between −0.6 and −0.3 mL/min) and 11% of the patients experienced adverse events, leading to treatment discontinuation in only one patient.

Several additional reports have described successful outcomes by using sofosbuvir-based regimens in kidney transplant recipients [154, 170–173, 175, 176].

However, approximately 80% of sofosbuvir is excreted by renal route in form of dephosphorylation-derived nucleoside metabolite GS-331007 [89]. Due to the higher exposure (up to 20-fold) to GS-331007, special cautions should be adopted in KTRs, especially in those with uncomplete recovery of renal function after transplantation [177].

The phase 3, open-label MAGELLAN-2 study evaluated a 12-week course of the pangenotypic regimen glecaprevir/ pibrentasvir in 20 KTRs [174]. A high rate of SVR was confirmed as well as its safety profile. The extent of the drug interaction with calcineurin inhibitors (see Statement 7.4)

and the need of therapeutic drug monitoring is counterbalanced by the fact that this regimen can be used independent of renal function, as renal excretion is not the preferred mechanism of elimination.

Overall, these studies confirmed the high rate of viral eradication also in the setting of kidney transplantation without significant incidence of graft rejection. Notwithstanding, a trend toward decrease in CNI trough levels has also been reported in most studies dealing with sofosbuvir-based DAA therapy in KTRs with the need of CNI dose adjustment after beginning DAA therapy [177]. Recently, Fernandez-Ruiz focused on the impact of sofosbuvir-based regimens on the pharmacokinetics of immunosuppressive drug levels in 49 KTRs and observed marked increased in dose requirements of calcineurin inhibitors (CNI) and everolimus to maintain blood concentrations as well as a significant decrease in eGFR and increase of proteinuria during the first year after treatment [176]. The possibility that HCV clearance, as described in other settings, could paradoxically favor alloimmune-mediated injury or that abnormal tacrolimus pharmacokinetic could lead to drug underexposure are the most attractive hypotheses and deserves peculiar care also during mid-term post eradication follow up [178].

Statement 7.3 Timing of DAA therapy—i.e. to treat before or after kidney grafting- should be individualized in each patient, by balancing individual clinical conditions and the need to shorten time on waiting list. The decision to delay treatment after kidney transplant must take into account the availability of active national program for the allocation of HCV positive organs.

Rationale

The better timing of DAA therapy for KTRs (before grafting or after successful kidney transplantation) remains a still unresolved issue [179]. Recent studies in ESRD patients with genotype 1 or 4 HCV infection receiving either grazoprevir/elbasvir [151], or ombitasvir/paritepravir/dasabuvir [150], have shown SVR in the majority of dialysis patients with a good safety profile. New options for these patients comes from the multicenter, open label, phase-3 trial with the pangenotypic combination of glecaprevir/ pibrentasvir for 12 weeks [152]. Among 104 patients with severe renal impairment and/or dependence on dialysis, SVR rate was 98%. Adverse events and serious adverse events were reported in 24% and 10% of the patients respectively leading to treatment discontinuation in four cases (3.8%) [152]. Overall, treating ESRD patients before kidney transplantation seems to be a good opportunity, by possibly avoiding

Table 7 Studies that have evaluated DAAs in kidney transplant recipients (KTRs)

Author [reference]	Year	Patients (Genotype)	Therapy	Duration (weeks)	SVR (%)	Adverse events	Graft function
Kamar [167]	2015	25 KTRs (76% genotype 1)	SOF-based	12–24	100	None	3 pts had eGFR decline ≥ 10 mL/min
							Decrease in TAC TL
Sawinski [168]	2016	20 KTRs (88% genotype 1)	SOF-SMV	12	100	None	Stable graft function
							45% required CNI dose adjustment
Lin [169]	2016	24 KTRs (58% genotype 1a)	SOF-based	12	91	46%, none required therapy discontinuation	Stable graft function
							2 pts (8.3%) required CNI dose adjustment
Beinhardt [170]	2013	8 KTRs (genotype 1,4)	SOF-based	12	100	50%, no severe AEs	Stable graft function
							1 pt (12.5%) required CNI dose adjustment
Lubetzky [171]	2017	31 KTRs (90% genotype 1)	SOF+LDV	12–24	97	None	Stable graft function in all but 2 pts whose eGFR reduced to < 20 mL/min
							Increase in proteinuria in 19%
Colombo [172]	2017	114 KTRs (genotype 1,4)	SOF+LDV	12–24	100	11%	eGFR decline from −0.6 to −0.3 mL/min
							2% clinical worsening
Morales [173]	2017	32 KTRs (91% genotype 1)	SOF+LDV	8–24	96	1 borderline rejection; 4 unrelated deaths	25% CNI dose adjustement
							Stable graft function
Reau[a] [174]	2017	20 KTRs (genotype 1–6)	GLE/PIB	12	98	Rare (1 sinusitis, 1 hepatic abnormality)	Slight reduction in TAC doses needed
Fernandez [175]	2017	103 KTRs (83% genotype 1)	SOF-based±RBV (n=93) PrOD±RBV (n=10)	12–24	98	3 rejection; 55% CNI dose adjustement	16% increase in creatinine
Saxena [153]	2017	60 KTRs (90% genotype 1)	SOF based	12–24	94.5	2 rejection	No specific data
Fernandez-Ruiz [176]	2018	49 KTRs (80% genotype 1)	SOF-based (47/49, 96%)	12–24	95.8	none	Significant decline in eGFR in the post-SVR follow-up period

SOF sofosbuvir, *SMV* simeprevir, *LDV* ledepasvir, *GLE/PIB* glecaprevir/probentasvir, *RBV* ribavirin, *PrOD* paritaprevir/ritonavir/ombitasvir+dasabuvir, *eGFR* estimated glomerular filtration rate, *TAC* tacrolimus, *CNI* calcineurin inhibitors, *SVR* sustained virologic response

[a]Data available only in abstract form

detrimental interference of DAA with immunosuppressive agents in the post-transplant setting.

However, this strategy exclude HCV+ patients on dialysis from the program of kidney transplantation from HCV infected donors (D+R+). In fact, HCV+ transplant candidates who were not treated while on the waiting list have the option of listing for a HCV+ kidney allocation. The individual benefit gained from this policy is that it reduced patients' time on the deceased donor waiting list owing the relatively few patients competing for a HCV+ kidney. In a study of the UNOS database from 1995 to 2009, Kucirka et al. found that recipients of HCV+ kidneys waited 310 days fewer than the average waiting times at

their center and 395 fewer days than counterparts who waited for HCV negative kidneys [180].

Excellent long-term results in terms of both patients and graft survival were also reported in a study that evaluated 195 HCV positive patients who received graft from HCV+ donors, as compared with 66 HCV+ receiving transplant from ideal HCV negative donors [181]. However, this program is weakened by the high rate of discard rate of HCV+ organs. McCauley et al., reported that only 37% of available HCV+ kidneys were transplanted from 2005 to 2014, with a discard rate of 67% compared to a usual rate of 20% for ideal organs [182]. Moreover, benefits resulting from the HCV+ for HCV+ program must be weighed against several concerns for transplanting HCV+ kidneys into HCV+ recipients. These concerns historically included the nearly universal transmission of the virus and the possible genotype superinfection as well as inferior patient and graft survival in patients who receive HCV+ compared to HCV− kidneys.

While the program HCV+ for HCV+ was associated with good results in the United States, data from Italian Transplant Registry are quite different with less than 1% of the total 10-year kidney transplants performed in HCV+ recipients from HCV+ donors according to the National 2015 Registry. This scenario probably reflects previous concerns about interferon application after transplant and it is expected to change substantially in the short-term period in view of the ability to treat efficiently HCV post-transplantation. Recently, the Italian National Center for Organ Transplantation has released official Italian guidelines for the utilization of HCV positive organs for transplantation (Fig. 2). Only systematic application of these rules could leads to actual improvement in kidney transplant rate with HCV+ organs, thus counterbalancing the concerns about the effectiveness of such a strategy.
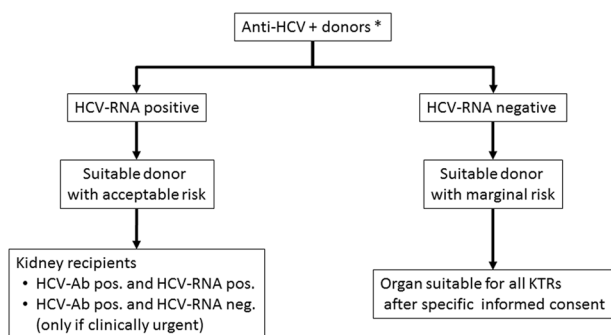
* Immediate HCV-RNA evaluation procedures are strongly suggested as soon as donors was known to be HCV positive. All recipients of an HCV positive organ (regardless of replicative status) must be strictly followed at 1, 2, 4, 8 and 12 weeks after transplant.

Fig. 2 Italian National guidelines for the evaluation of the eligibility of solid organ donors as per the State-Regions Conference (version 1.0; February 23, 2017)

However, the survival advantages of kidney transplant compared to dialysis patients strengthens the argument for delaying DAA treatment and listing for a HCV+ kidney. In a study by Sawinski et al., who hypothesize an algorithm for managing pre-transplantation patients with HCV, patients who received HCV+ kidneys waited approximately 484 days (1.3 years) significantly fewer than those who received HCV- kidneys [183].

Finally, two recent reports have shown good results of DAA therapy performed after kidney transplantation [184, 185]. SVR was obtained in 96% of HCV+ patients who received HCV+ kidneys and started DAA therapy in early post-transplant (median 125 days) [184] and in 100% of HCV negative ESRD subjects who received HCV+ kidneys receiving DAA therapy performed immediately after grafting [185]. These findings confirm that availability of DAA have definitely changed our perspectives in the management of HCV infected patients with ESRD.

In view of the association between HCV positivity and some specifically related conditions after kidney transplantation (diabetes, transplant glomerulopathy etc), data on the overall effects of treating HCV post-transplantation on patient and graft survival are warranted.

In the meanwhile, it appears wise to individualize treatment timing and schedules according to clinical criteria on the basis of availability of local organization favoring HCV positive donation.

Statement 7.4   DAA in kidney transplant recipients must be managed under strict collaboration between nephrologists and hepatologist. Careful baseline assessment of the degree of renal function, liver fibrosis staging, HCV genotypes, immunosuppressive schemes and concomitant therapies could safely address the choice of antiviral drug.

Rationale

The concomitant treatment with DAA and immunosuppressive drugs could expose the patients to drug–drug interactions (DDI) that should be actively prevented by correctly choosing therapeutic regimens, monitoring their effects during therapy and, when appropriate, performing therapeutic drug monitoring (TDM). The need to monitor immunosuppressive agent levels during DAA therapy, in fact, is highlighted by the observational HCV-TARGET cohort study: acute graft rejection occurred during or after cessation of therapy in 1.4% (6/415) of patients [154]. Although it is not clear if these episodes are a direct effect of the antiviral regimen, an accurate surveillance of the patients is mandatory.

The DDIs between sofosbuvir-based DAA treatments and immunosuppressive drugs (CNI, tacrolimus,

everolimus) have been previously described (Statement 7.2). In choosing the most appropriate associations of DAA and immunosuppressive agent, we should also consider that cyclosporine and tacrolimus increase daclatasvir area under the curve (AUC) by 40% and 5%, respectively although these changes are not clinically significant. On the other hand, daclatasvir does not cause clinically meaningful changes in CNI, mammalian target of rapamycin (mTOR) inhibitor, steroid, or mycophenolate levels. In healthy volunteers, coadministration of a single dose of cyclosporine with simeprevir resulted in a 19% increase in cyclosporine concentration and simeprevir concentration similar to historical data [186]. Moreover, the phase 2 SATURN study reported that HCV-infected liver transplant recipients with genotype 1b infection taking simeprevir plus daclatasvir and ribavirin concomitantly with cyclosporine experienced a five-fold increase in plasma simeprevir exposure compared with phase 3 trials of simeprevir in the absence of cyclosporine [187]. This interaction may be caused by cyclosporine's inhibition of OATP1B1, P-gp, and cytochrome P450 3A (CYP3A). Given these findings, simeprevir should not be coadministered with cyclosporine.

Coadministration of a single dose of tacrolimus with simeprevir in healthy volunteers did not result in a notable change in tacrolimus concentration [186]. Conversely, an interim analysis of the SATURN study data noted an 85% increase in plasma simeprevir exposure when used concomitantly with tacrolimus compared with historical data [187, 188]. Based on phase 1 studies, a two-fold increase in simeprevir concentration is unlikely to be clinically significant. Clinicians may consider use of sofosbuvir plus simeprevir in patients receiving tacrolimus with TDM, particularly in those expected to be unsuitable for ribavirin (eg, patients with impaired renal function or anemia) or in patients who are proton pump inhibitors dependent, as these agents attenuate ledipasvir absorption.

Velpatasvir is a substrate for CYP3A4, CYP2C8, and CYP2B6, a weak inhibitor of P-gp and OATP transporters, and a moderate inhibitor of the BCRP membrane transporter. As such, velpatasvir is moderately affected by potent inhibitors and, to a greater extent, by potent inducers of enzyme/drug transporter systems [189]. Based on this profile, which is similar to ledipasvir, clinically significant drug–drug interactions would not be expected for co-administration of sofosbuvir/velpatasvir with common immunosuppressive agents (eg, tacrolimus, cyclosporine, corticosteroids, mycophenolate mofetil, or everolimus). Based on the metabolism of grazoprevir and elbasvir, a 15-fold increase in grazoprevir AUC and a two-fold increase in elbasvir AUC can be expected with cyclosporine co-administration. Therefore, this combination should be avoided. Since a 40–50% increase in tacrolimus level is predicted during co-administration with grazoprevir, no dosing adjustments seem to be required, but tacrolimus levels should be carefully monitored.

Glecaprevir and pibrentasvir are inhibitors of P-gp, BCRP, and OATP 1B1/3 and a weak inhibitors of CYP P450 3A and UGT 1A1 in vivo. Other significant inhibitions are not expected. Cyclosporine inhibits P-gp and BCRP and a five-fold increase of glecaprevir AUC is expected with higher doses cyclosporine. Consequently, this regimen is not recommended for use in patients requiring stable cyclosporine doses > 100 mg per day. If the combination is unavoidable, however, use can be considered if the benefit outweighs the risk adopting a close clinical monitoring. By contrast, a moderate 1.45-fold increase in tacrolimus AUC is expected. Therefore, the combination of glecaprevir/pibrentasvir with tacrolimus should be used considering an accurate therapeutic drug monitoring of tacrolimus and an accordingly dose adjustment [190].

In summary, the interaction of DAA agents and CNI is complex and unpredictable without available studies of DDIs. A summary of drug interactions between CNI and DAA with recommended dosing is provided in Table 8.

Particular attention should be addressed to the special population of HIV/HCV co-infected KTRs, where the DDI surveillance must include also the antiretroviral regimens. In these patients, DAA regimens and/or antiretroviral drug switches, when needed, should be planned in a multidisciplinary fashion including the nephrologist, the hepatologist and the HIV specialist.

The use of the online drug interaction charts by the Department of Pharmacology at the University of Liverpool is therefore strongly encouraged [191, 192].

Conclusion

A strict collaboration among different healthcare professional involved in the care of CKD patients with HCV infection is mandatory in order to timely identify this population and tailor the most appropriate treatment based on the patient's clinical condition. To this aim, we recommend the multidisciplinary approach reported in Fig. 3. Nephrologist must screen all patients at their first visit for HCV infection with anti-HCV Ab assay. In those positive, a viral load must be required with, possibly, the determination of the HCV genotype. Once nephrologist has completed the staging of CKD, the patient must be sent to hepatology consultation to perform staging of hepatic disease and evaluate eligibility to DAA treatment. The choice of DAA to administer remains in charge to the hepatologist, but discussion with nephrologist about concurrent therapy, renal involvement and comorbidities is recommended in order to better select the most appropriate DAA regimen. Monitoring of DAA response remains a specific competence of hepatologist

Table 8 DAA interactions with calcineurin inhibitors (Modified by AASLD/IDSA HCV Guidance: Recommendations for Testing, Managing, and Treating Hepatitis C Sept. 21, 2017)

	CYCLOSPORIN	TACROLIMUS
SOF	4.5-fold ↑ in SOF AUC, but GS-331,007 metabolite unchanged; no a priori dose adjustment	No interaction observed; no a priori dose adjustment
Ledipasvir	No data; no a priori dose adjustment	No data; no a priori dose adjustment
PrOD	5.8-fold ↑ in CSA AUC; modeling suggest using 1/5 of CSA dose during PrOD treatment, monitor CSA levels and titrate CSA dose as needed	57-fold ↑ in TAC AUC; modeling suggests TAC 0.5 mg every 7 days during PrOD treatment, monitor TAC levels and titrate TAC dose as needed
EBR/GZR	15-fold ↑ in GZR AUC and two-fold ↑ in EBR AUC; combination is not recommended	43% ↑ in TAC; no a priori dose adjustment
Velpatasvir	No interaction observed; no a priori dose adjustment	No data; no a priori dose adjustment
GLE/PIB	Five-fold ↑ in GLE AUC with higher doses (400 mg) of CSA; not recommended in patients requiring stable CSA doses > 100 mg/day	1.45-fold ↑ in TAC AUC; no a priori dose adjustment, monitor TAC levels and titrate TAC dose as needed
SOF/VEL/VOX	9.4-fold ↑ in VOX AUC; combination is not recommended	No data; no a priori dose adjustment

AUC area under the curve, *CSA* cyclosporine, *TAC* tacrolimus, *SOF* sofosbuvir, *PrOD* paritaprevir/ritonavir/ombitasvir + dasabuvir, *EBR/GZR* elbasvir/grazoprevir, *GLE/PIB* glecaprevir/pibrentasvir, *SOF/VEL/VOX* sofosbuvir/velpatasvir/voxilaprevir
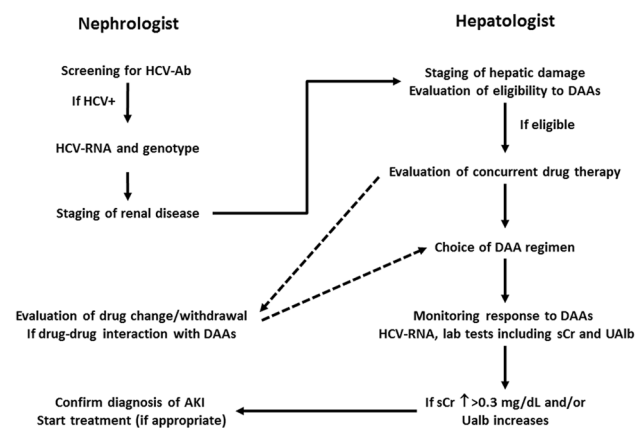
Fig. 3 Multidisciplinary model of care for the treatment of CKD patients with HCV infection

but he/she is required to include in the panel of laboratory data at least serum creatinine and albuminuria, measured as either dipstick, albumin/creatinine ratio on morning void or 24-h excretion. In the presence of signal of acute renal damage (increase of serum creatinine > 0.3 mg/dL and/or presence or worsening of albuminuria), hepatologist must refer the patient to the nephrologist to confirm diagnosis of AKI and eventually to implement specific treatment.

Compliance with ethical standards

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