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), Italian Society of Nephrology (SIN).

MANAGEMENT OF HEPATITIS C VIRUS INFECTION IN PATIENTS WITH CKD:
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CKD Classification[1] and estimated age-standardized prevalence in Italian general population[2]

		Persistent albuminuria categories		
		A1 (Normal) • *ACR <30 mg/g* • *Ualb <30 mg/24h* • *Uprot <150 mg/24h* • *Dipstick Negative*	**A2 (Moderate)** • *ACR 30-300 mg/g* • *Ualb 30-300 mg/24h* • *Uprot 150-500 mg/24h* • *Dipstick Trace to 1+*	**A3 (Severe)** • *ACR >300 mg/g* • *Ualb >300 mg/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/creatinine ratio; Ualb, 24h albuminuria; Uprot, 24h proteinuria. Colors refer to global prognosis: 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.

1 KDIGO Guideline *Kidney Int Suppl* 2013
2 De Nicola L, et al. *Nephrol Dial Transplant*. 2015

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Laboratory and clinical parameters suggesting referral to nephrologist

GFR <30 ml/min/1.73 m² *(independently from albuminuria level)*
Severe Albuminuria * *(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

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

MANAGEMENT OF HEPATITIS C VIRUS INFECTION IN PATIENTS WITH CKD:
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HCV-associated Kidney Diseases: clinical manifestations and suggested pathogenetic factors

Kidney disease	Clinical manifestations	Hypothetical pathogenetic factors
Cryoglobulinemic membranoproliferative glomerulonephritis (MPGN)	Nephritic syndrome, Nephrotic syndrome	Cryoglobulin deposition in glomerular capillaries, mesangium, and urinary space; mesangial deposits of immune complexes including HCV antigens, Ig and C3-C4
Non-cryoglobulinemic MPGN	Nephritic syndrome, Nephrotic syndrome	Mesangial deposits of immune complexes (HCV antigens, Ig, and complement components)
Membranous Nephropathy	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-ag, Ig, C3-C4)
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 C3-C4)
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

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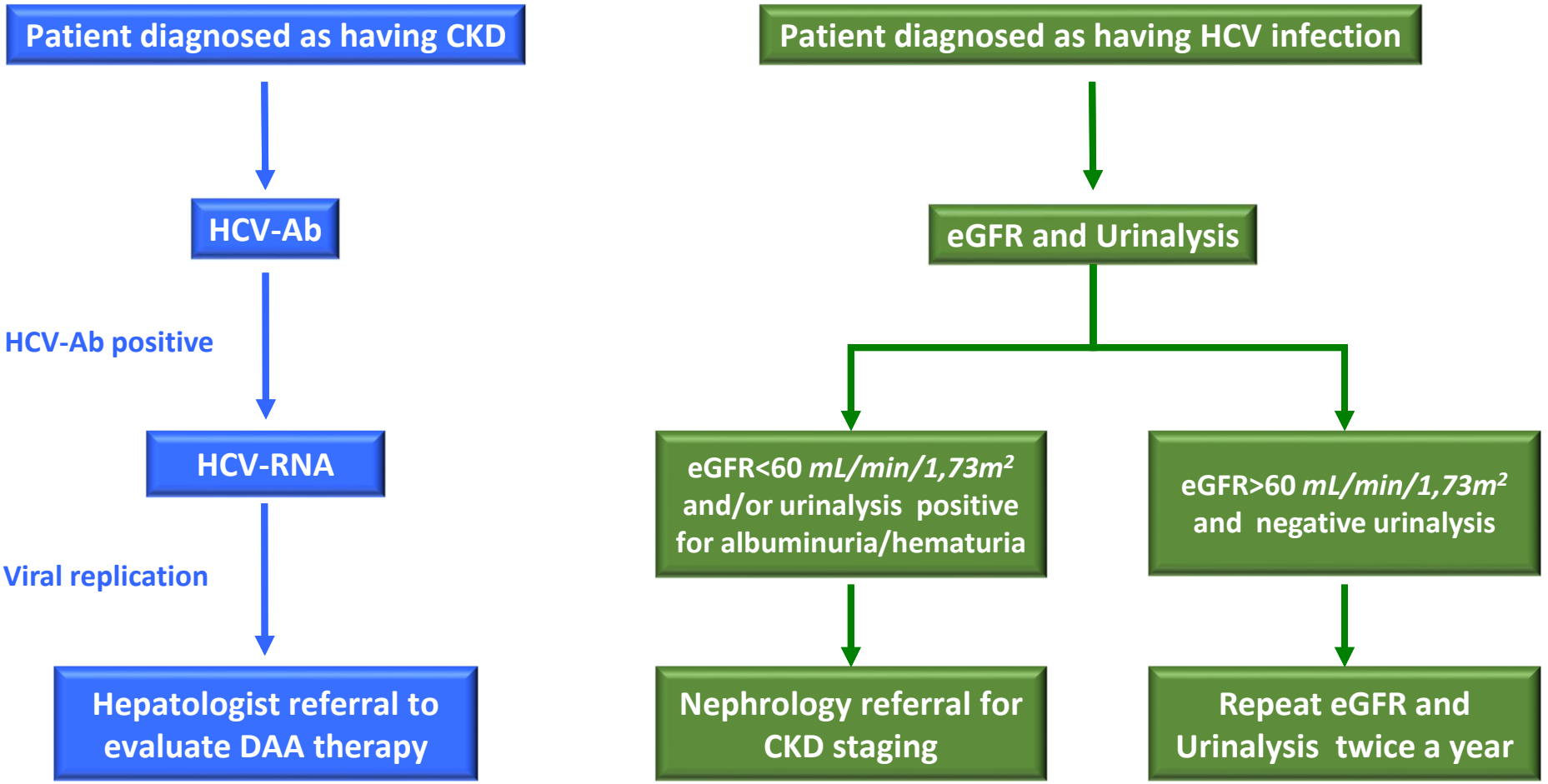
Recommended screening for CKD and HCV infected patients.



Prevalence of HCV-Ab positive serologic status among patients on hemodialysis

Author	Country	Year	N HCV+/N total	Prevalence of anti-HCV Ab
Alashek W	Libya	2012	2,382/7,659	31.1%
Garcia-Agudo	Spain	2013	708/12,472	5.6%
Goodkin (DOPPS)	UK	2013	85/2,575	3.3%
Goodkin (DOPPS)	US	2013	1,766/20,534	8.6%
Goodkin (DOPPS)	Italy	2013	413/2,581	16.0%
Goodkin (DOPPS)	Japan	2013	1,278/7,607	16.8%
Ummate	Nigeria	2014	15/100	15.0%
Lioussfi	Morocco	2014	40/67	59.7%
Vidales-Braz	Brazil	2015	58/318	18.2%
Duong	Vietnam	2015	8/113	7.0%
Malhotra	India	2016	88/262	33.5%

Alashek W, *BMC Infect Dis* 2012; 12: 265; Garcia-Agudo R, *Nefrologia* 2013; 33: 188-195; Goodkin D, *Am J Nephrol* 2013; 38: 405-412; Ummate I, *Pan Afr Med J* 2014; 19: 305; Lioussfi Z, *Saudi J Kidney Dis Transplant* 2014; 25: 672-679; Vidales-Braz B, *Virol J* 2015:12:8; Duong C, *BMC Public Health* 2015; 15: 192; Malhotra R, *J Nat Sci Biol Med* 2016; 7: 72-74

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Infection control practices aimed at preventing transmission of HCV infection in hemodialysis 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 Ab testing (every 6 months), ALT testing (monthly) for susceptible patients
Infection control training and education
Regular audits to ensure improved adherence to recommended practice

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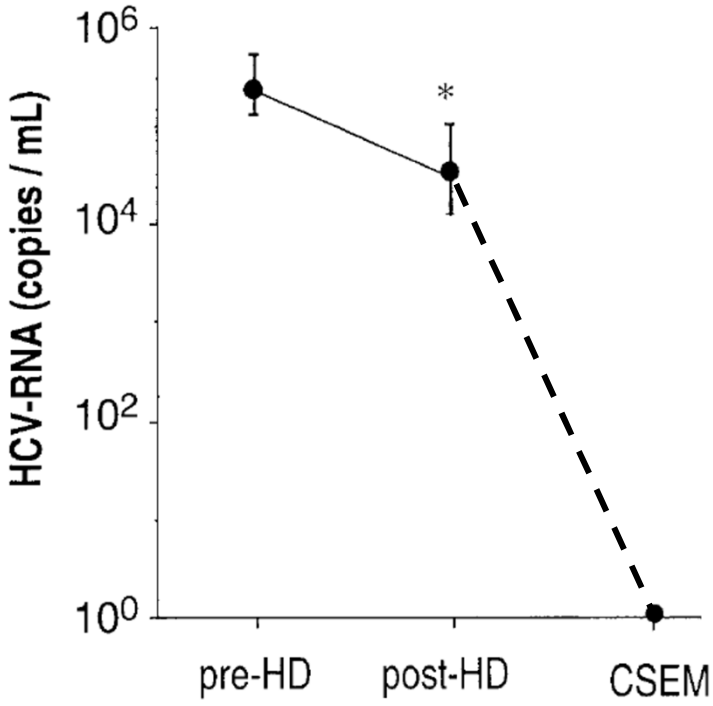
- **Isolation of hemodialysis patients with HCV infection is not suggested**
- **Dedicated dialysis machines for hemodialysis patients with HCV are not recommended.**

HCV-RNA was measured on samples drawn before and after high-flux polysulfone membrane and in spent dialysate (CSEM) extracted in a sterile fashion in 20 HD patients



Noiri E, AJKD 2001

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HCV Treatment Regimens approved in 2018

Genotype	Pangenotypic regimens		Genotype-specific regimens		
	SOF/VEL	GLE/PIB	GZR/EBR	PrOD	PrO
Genotype 1a	Yes	Yes	Yes	Yes	No
Genotype 1b	Yes	Yes	Yes	Yes	No
Genotype 2	Yes	Yes	No	No	No
Genotype 3	Yes	Yes	No	No	No
Genotype 4	Yes	Yes	Yes	No	Yes
Genotype 5	Yes	Yes	No	No	No
Genotype 6	Yes	Yes	No	No	No

Impact of Renal Impairment on DAA Pharmacokinetics

Change in exposure compared to healthy subjects with normal renal function	Mild impairment (eGFR = 60–89 mL/min/1.73m^2)	Moderate impairment (eGFR = 30–59 mL/min/1.73m^2)	Severe impairment (eGFR = <30 mL/min/1.73m^2)
Ombitasvir	↔	↔	↔
Paritaprevir	↑ ≤20%	↑ ≤37%	↑ ≤50%
Dasabuvir	↑ ≤20%	↑ ≤37%	↑ ≤50%
Ledipasvir	NA	NA	Change not clinically relevant
Sofosbuvir **GS-331007**	**↑ 61%*** **↑ 55%***	**↑ 107%†** **↑ 88%†**	**↑ 171%** **↑ 451%**
Velpatasvir	NA	NA	↑ 50%
Grazoprevir	NA	NA	↑ 65%
Elbasvir	NA	NA	↑ 86%
Glecaprevir	↑ ≤56%	↑ ≤56%	↑ ≤56%
Pibrentasvir	↑ ≤56%	↑ ≤56%	↑ ≤56%

Khatri A, *et al. Hepatology* 2014; 60 (Suppl) :320A; Harvoni, (July 2016) , Maviret (July 2017) Epclusa (July 2017)
Summaries of Product Characteristics Yeh WW, *et al. Hepatology* 014; 60(Suppl 4):1940 (poster presentation)..

HCV Treatment in Patients with Renal Impairment

- **eGFR ≥30 ml/min/1.73 m² :**
  - Treat according to the general recommendations

- **eGFR <30 ml/min/1.73 m² or ESRD:**
  - Prefer RBV free regimens
  - Glecaprevir/pibrentasvir for 8, 12 or 16 weeks (all genotypes)
  - Grazoprevir/elbasvir for 12-16 weeks (genotypes 1a, 1b and 4)
  - Ombitasvir/paritaprevir/ritonavir + dasabuvir for 12-24 weeks (genotype 1a, 1b)
  - Ombitasvir/paritaprevir/ritonavir for 12 weeks (genotype 4)
  - Sofosbuvir should be used with caution, only if an alternative treatment is not available

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DAA Regimens for specific genotype of HCV in patients with CKD stage 4-5

Combination regimen	GT1a	GT1b	GT2	GT3	GT4	GT5-6
PrOD ± RBV	12-24* wks + RBV	12 wks	NO	NO	NO	NO
PrO ± RBV	NO	NO	NO	NO	12 wks + RBV	NO
GZR/EBR ± RBV	12-16 wks° ± RBV	12 wks	NO	NO	12-16 wks° ± RBV	NO
GLE + PIB	8-12§ wks	8-12§ wks	8-12§ wks	8-16§# wks	8-12§ wks	8-12§ wks

PrOD, paritaprevir/ritonavir/ombitasvir/dasabuvir, GZR/EBR, grazoprevir/elbasvir; GLE/PIB, glecaprevir/pibrentasvir; RBV, ribavirin

*** 24 weeks in patients with CPT A cirrhosis**
° 16 weeks in patients with HCV RNA >800.000 IU/mL or NS5A RAS
§ 12 weeks in patients with CPT A cirrhosis
 # 16 weeks in patients with a previous failure to PegIFN or SOF

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

Author (year)	Patients (Genotype)	Therapy	Duration (weeks)	SVR	Adverse events	Graft function
Kamar (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 (2016)	20 KTRs (88% genotype 1)	SOF-SMV	12	100%	none	• Stable graft function • 45% required CNI dose adjustment
Lin (2016)	24 KTRs (58% genotype 1a)	SOF-based	12	91%	46%, none required therapy discontinuation	• Stable graft function • 8.3% required CNI dose adjustment
Beinhardt (2013)	8 KTRs (genotype 1,4)	SOF-based	12	100%	50%, no severe AEs	• Stable graft function • 12.5% required CNI dose adjustment
Lubetzky (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 (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 (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 (2017)	20 KTRs (genotype 1-6)	GLE/PIB	12	98%	1 sinusitis, 1 hepatic abnormality	• Slight reduction in TAC doses needed
Fernandez (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 (2017)	60 KTRs (90% genotype 1)	SOF based	12-24	94.5%	2 rejection	• No specific data
Fernandez (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

MANAGEMENT OF HEPATITIS C VIRUS INFECTION IN PATIENTS WITH CKD:
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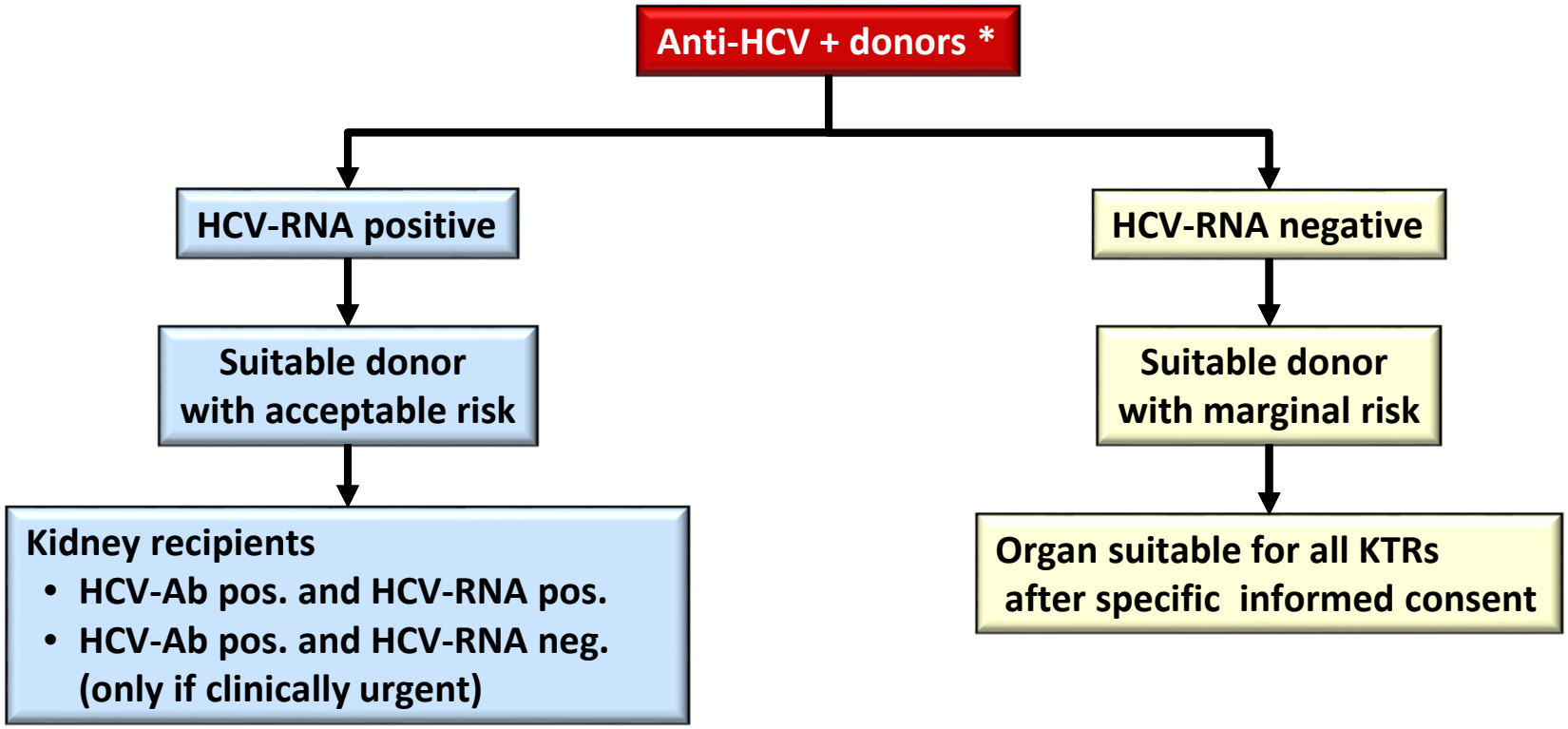
Italian National guidelines for the evaluation of the eligibility of solid organ donors as per the State-Regions Conference (version 1.0; February 23, 2017)



* 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.

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DAA Interactions with Calcineurin Inhibitors.

	CYCLOSPORIN	TACROLIMUS
SOF	4.5-fold ↑ in SOF AUC, but GS-331007 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 2-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	5-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.

Modified by AASLD/IDSA HCV Guidance: Recommendations for Testing, Managing, and Treating Hepatitis C Sept. 21, 2017

MANAGEMENT OF HEPATITIS C VIRUS INFECTION IN PATIENTS WITH CKD:
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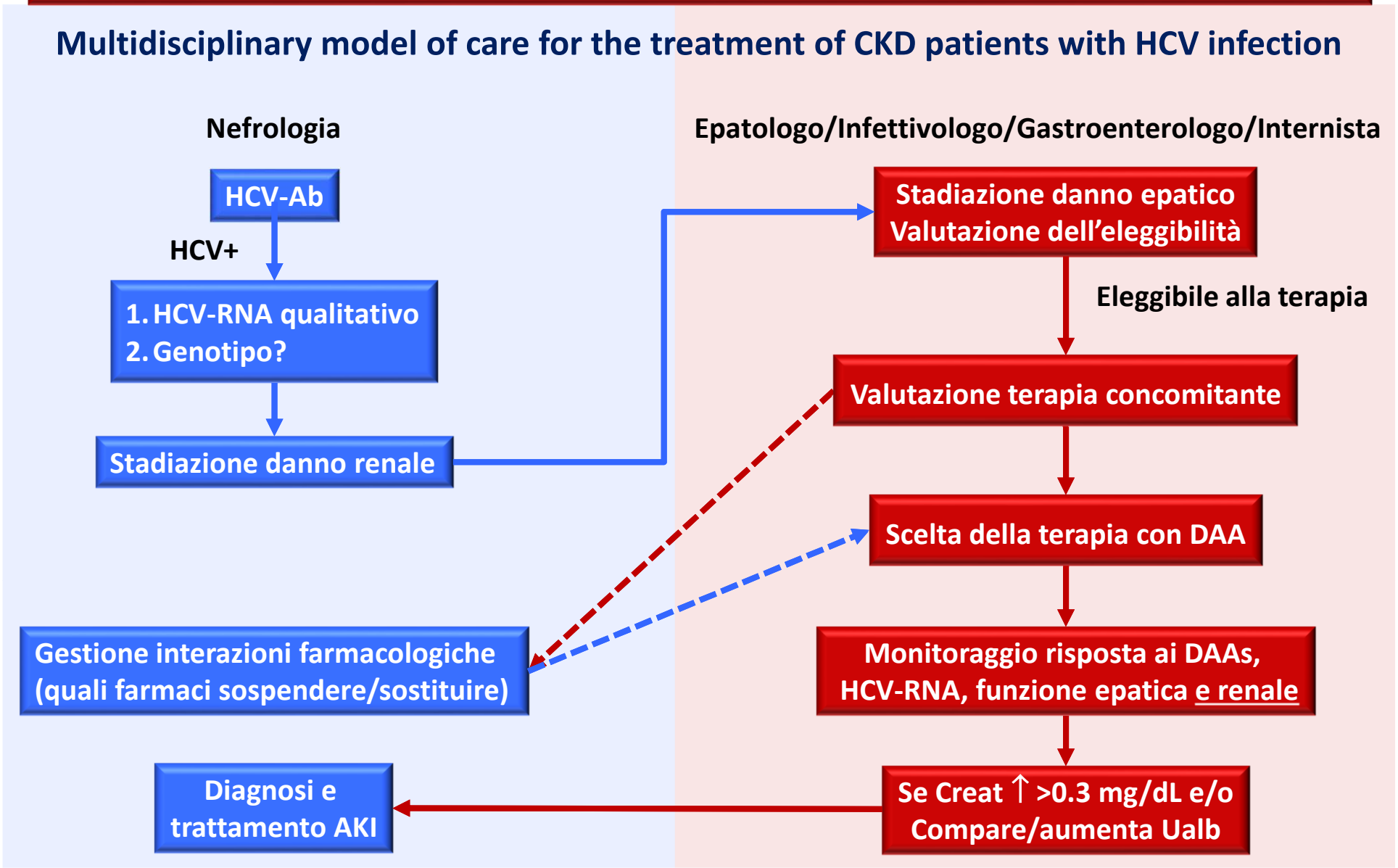
Multidisciplinary model of care for the treatment of CKD patients with HCV infection



MANAGEMENT OF HEPATITIS C VIRUS INFECTION IN PATIENTS WITH CKD:
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MANAGEMENT OF HEPATITIS C VIRUS INFECTION IN PATIENTS WITH CKD:
Position statement of Joint Committee of AISF, SIMI, SIMIT, SIN

1. 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.

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

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

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

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

MANAGEMENT OF HEPATITIS C VIRUS INFECTION IN PATIENTS WITH CKD:
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2. 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 d be screened for HCV infection.

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.

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.

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).

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3. HCV 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.

Statement 3.2 Screening for hepatitis C virus 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.

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).

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

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4. 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.

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.

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.

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5. 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

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

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

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.

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6. Treatment of chronic Hepatitis C virus in chronic kidney disease patients

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

Statement 6.2. The presence of CKD influences DAA Pharmacokinetics

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

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

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

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6. 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.

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

Statement 7.3 Timing of DAA therapy – i.e. to treat before or after kidney grafting- should be individualized in each patient, 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.

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.