Digestive and Liver Disease 51 (2019) 10–23

Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Position Paper

AISF position paper on HCV in immunocompromised patients

Italian Association for the Study of the Liver (AISF)[1,2]

ARTICLE INFO

Article history:
Received 22 May 2018
Accepted 18 September 2018
Available online 1 October 2018

Keywords:
HCV
Immunocompromised patients
Organ transplant

ABSTRACT

This report summarizes the clinical features and the indications for treating HCV infection in immunocompromised and transplanted patients in the Direct Acting Antiviral drugs era.

1. Introduction

In the last 15 years many immune-modulating therapies have been introduced. Even if most lack direct hepatic toxicity, patients with serological signs of current virus C- or either overt or anamnestic B-related infection (HCV and HBV respectively) are at a potential risk for reactivation. Concerning HCV, the liver disease is usually exacerbated and more rapidly evolutive in immunosuppressed patients and reactivation can affect the treatment plan [1]. This report summarizes the indications developed in a consensus conference held in Italy in 2017 and aimed to define the clinical features and management of viral hepatitis among specific groups of immunocompromised patients and special populations.

2. Methodology

A meeting promoted by the Italian Association for the Study of the Liver (AISF) was planned to identify items to be discussed and answered with consensus statements; for each area a working group was formed, composed by at least four experts guided by a chairman.

The scientific committee selected four clinical questions, dealing with both clinical and controversial issues (Table 1). Emerging recommendations were rated according to GRADE system (Table 2) [2,3].

The statements, together with a literature review presentation, were discussed before the Consensus Conference. The process ended with a formal meeting held in Turin on December 15–16th, 2017. A jury of clinical specialists including, epidemiologists, methodologists, patient representatives, nurses and ethicists was selected. As stated in the jury regulation, member of the working group voted only the statements of the other groups guaranteeing the principle of jury's independence. The area of interest of each working group was clearly defined without any overlap and thus all those who had the right to vote were by no means involved in the selection, preparation, and discussion of topics and statements.

During general sessions, topics and statements proposed to answer each question were presented. A general discussion was held to refine statements and identify possible improvements. At the end of the general session, the revised statements were presented and voted electronically by the jury and all members not involved in their preparation (two levels of agreement: agree/disagree).

All promoters, members of the scientific board, working groups, and jury invited to participate to the Consensus Conference were asked to declare conflict of interests.

Table 1
Clinical questions.

Question number	
Q1	Which patients should be screened?
Q2	Who should be treated and how?
Q3	Who should be monitored and how?
Q4	How long should be treated and/or monitored?

3. Immunopathogenesis and general assessment

3.1. Immunopathogenesis

Immunopathogenesis is summarized in Appendix C [4–12].

[1] Authors (Appendix A).
[2] Jury (Appendix B).

https://doi.org/10.1016/j.dld.2018.09.022
1590-8658/

Table 2
Grading of recommendations, assessment, development and evaluation.

Grading of evidence	Notes	Symbol
High quality	Further research is very unlikely to change our confidence in the estimate of effect	A
Moderate quality	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate	B
Low or very low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Any estimate of effect is uncertain	C
Grading recommendation	**Notes**	**Symbol**
Strong recommendation warranted	Factors influencing the strength of the recommendation included the quality of evidence, presumed patient-important outcomes, and cost	1
Weaker recommendation	Variability in preferences and values, or more uncertainty: more likely a weak recommendation is warranted Recommendation is made with less certainty: higher cost or resource consumption	2

For grading evidence the symbol is a letter: A or B or C.
For grading recommendations the symbol is a number: 1 or 2.

3.2. Epidemiology

In the last 25–30 years, HCV epidemiology in Italy has shown a progressive decline in new infections, mainly due to the change of major drivers (i.e. iatrogenic transmission, drug abusers) with a shift of the hazard from general to special populations with risky behaviours [13,14]. At present the prevalence of HCV infection in Italy is not known: a recent study conducted on 4907 subjects enrolled in 5 metropolitan area showed a 2.3% anti-HCV prevalence with HCV-RNA positivity in 74.1% of cases [14]. Interestingly, the anti-HCV prevalence in individuals born after 1954 ranges between 0.2 to 1.2, confirming a higher prevalence in older population [14–16].

3.3. Virology

The HCV genome consists of approximately 9600 nucleotides codifying a polyprotein of about 3000 amino acids, cleaved by host and viral proteases into three structural proteins (Core and Envelope glycoproteins E1 and E2) and seven non-structural proteins (p7, NS2, NS3, NS4A, NS4B, NS5A, and NS5B), required for viral processing, replication and particle assembly. HCV enters the cell after interaction with high affinity receptors (hCD81, SR-B1, LDLR, DC-SIGN and L-SIGN) not exclusive of hepatocytes. The positive-sense single-stranded RNA genome in the cytoplasm serves as messenger RNA and template for replication, microRNA-122 dependent (responsible for the almost hepatocyte-exclusive HCV replication) [17,18]. Virion morphogenesis implies a major interaction with apolipoproteins (Apo A, C, E and B) and VLDL [6–8] and HCV circulates as lipo-viro-particles. At present, there are no evidences for the production of an intrahepatic viral reservoir [19].

Once viral infection has been cleared, either spontaneously or by antiviral therapy, HCV reactivation (HCVr) does not recur. This event has been reported only anecdotally among patients with previously undetectable HCV-RNA, though as measured by assays with low sensitivity (600 IU/ml) [20]. On the contrary, reinfection with another genotype may occur because of lack of completely sterilizing immunity, in spite of a specific T cell response, which protects against reinfection from the same HCV strain [21].

3.4. Pathogenesis and extrahepatic manifestations

HCV infection is often associated with extrahepatic manifestations, which can be classified according to the principal underlying pathogenetic process as autoimmune, inflammatory, metabolic or neoplastic. HCV can alter the cellular functions just by receptorial interaction, as it occurs when HCV coated by C3d engages CD81 on the surface of B lymphocytes, leading to their activation with autoantibodies and cryoglobulins production [22]. Cryoglobulinemic vasculitis is the most relevant extrahepatic disease related to chronic HCV infection and represents a model for the development of neoplastic haematologic processes caused by this virus [23]. In the liver, HCV causes a dysregulation of lipid homeostasis favouring tryglicerides accumulation [24]. In addition HCV infection favours both hepatic and peripheral insulin resistance, which can drive further steatosis [25]. Hepatic steatosis, affecting approximately half of HCV-infected individuals, can contribute to liver disease progression and, in presence of other co-factors (i.e. drugs), acting synergistically thus amplifying liver injury [26].

3.5. Clinico-virologic assessment

Serum HCV-RNA must be tested (by assays of adequate sensitivity: limit of detection $\leq$15 IU/ml) in all anti-HCV positive individuals to prove ongoing HCV infection (about 25% anti-HCV positive individuals show undetectable viremia, suggesting clearance of the infection) [27]. HCV genotyping (GT) identifies different disease patterns (risk for hepatitis flares in long lasting indolent GT 2 infections; severe steatosis in GT 3 infected patients), and might warrant (with subtyping for GT1) individualized antiviral treatment.

The causal relationship between HCV infection and liver disease should be established in each patient, excluding other causes of liver damage. Assessment of liver disease stage is needed, independently of ALT levels, since it affects prognosis. Non invasive techniques, such as liver stiffness and biomarkers determinations, perform well in the identification of cirrhosis or absence of fibrosis, but are less accurate in defining the intermediate stages of fibrosis [28].

3.6. Risk of reactivation

HCVr is defined as a 1 log increase in HCV-RNA levels over baseline. Acute exacerbation of HCV hepatitis is defined as a 3-fold or greater increase over basal in serum ALT level in the absence of other causes as infiltration of the liver by cancer, use of hepatotoxic drugs, HBV reactivation or other systemic viral infections.

HCVr during immunosuppressive therapy has been reported in about 30% of patients, particularly those with haematologic malignancies and/or treated with Rituximab [29–32]. At present, consistent evidences of reactivation of latent HCV infection in extrahepatic organs are missing, and HCV biology makes this hypothesis unlikely [18,23].

HCVr can be associated with ALT flares occurring during treatment or within 3 months from treatment discontinuation: the outcome of these flares is less severe than that of HBV-related reactivations [31–34]. Occurrence of hepatic decompensation appears to be rare, but a significant proportion of patients has to discontinue

chemotherapy [31,32,35]. Moreover, the natural course of chronic hepatitis C can be worsened by anti-cancer treatment [36–38].

3.7. Management and strategies

The goal of antiviral therapy is to cure HCV infection and to prevent hepatic cirrhosis, its complications and severe extrahepatic manifestations. The endpoint of antiviral therapy is undetectable serum HCV RNA by a sensitive assay (≤15 IU/ml) 12 or 24 weeks (SVR12 or 24) after the end of treatment [27]. In patients with advanced fibrosis and cirrhosis, HCV eradication reduces, but does not abolish the occurrence of decompensation and HCC risk.

Direct Acting Antiviral drugs (DAAs) inhibiting HCV replication acting on viral proteins revolutionized HCV treatment. At present 3 classes of DAAs are authorized: (1)***anti-NS3-4A inhibitors*** (simeprevir, ritonavir boosted paritaprevir, grazoprevir, glecaprevir, voxilaprevir); (2)***anti-NS5A inhibitors*** (daclatasvir, ledipasvir, ombitasvir, velpatasvir, elbasvir, pibrentasvir); (3) ***anti-NS5B inhibitors*** (dasabuvir, a non-nucleoside inhibitor and sofosbuvir, a nucleotide inhibitor). DAAs should never be administered as monotherapy, but always in combination to warrant a potent and multivalent antiviral activity, minimizing the emergence of resistant variants. HCV infection can be cleared by DAAs regimens in >95% of treated patients, with slightly lower rates in decompensated liver disease [27].

Drug–drug interaction (DDIs) has to be carefully evaluated in each patient: for example, there are absolute contraindications for the combined use of any DAAs with carbamazepine and for sofosbuvir with amiodarone. Sofosbuvir should also be used with caution in patients with severe renal impairment (eGFR <30 ml/min/1.73 m^2). NS3-4A protease inhibitors should not be used in patients with Child–Pugh B decompensated cirrhosis or in compensated cirrhosis but with previous episodes of decompensation, and are contraindicated in Child–Pugh C patients [30].

DAAs are currently recommended in all HCV carriers with the only exclusion of patients with limited life expectancy due to non-liver-related comorbidities [27].

Data on the treatment of HCV infection in patients with cancer are limited, but show SVR rates comparable to those observed among non-neoplastic patients [38–40]. Therefore, considering that concomitant HCV infection increases morbidity which may interfere with cancer treatment and that its eradication could be helpful in the treatment of lymphoma [41–43], antiviral treatment should be considered in this subgroup of patients.

4. Oncology

4.1. Epidemiology

Prevalence of HCV infection in patients with solid cancer is similar to that observed in the general population (0.6–2.9%) and there is no association between HCV infection and risk to develop cancer, except for hepatocellular carcinoma [31].

Scientific associations (EASL, AASLD, ASCO, AISF) do not recommend testing patients who undergo chemotherapy. Recent studies reported that only 14% of oncologic patients undergo HCV infection testing in the United States, and a low sensitivity of the selective testing using a questionnaire on HCV risk factors in France [44,45]. Testing should be defined according to local HCV infection epidemiology, ideally within the framework of national plans, particularly among subjects with behaviours, exposures or conditions associated with an increased risk of infection [46].

4.2. Clinical impact

Risk of HCVr in patients with cancer on chemotherapy ranges between 5–10% and reactivation can rarely be symptomatic or fatal. It can occur after administration of specific chemotherapy regimens (bendamustine or purine analogs). Long term administration of high dose systemic corticosteroids may also increase the risk of reactivation and acute exacerbation [47].

Data on DAAs treatment are becoming available in this setting and SVR rates seem to be similar to those observed in HCV-infected patients without cancer. Antiviral therapy should be offered to cancer patients, except those with uncontrolled cancer and comorbidities associated with a life expectancy <12 months. Simultaneous antiviral and oncologic therapy may prevent delays in the administration of chemotherapy [38]. Management and strategies are the same applied in non-cancer patients. In patients who achieved SVR after DAAs, the continuation of chemotherapy or new chemotherapy cycles do not induce reactivation of HCV infection [48].

Questions

Q1. All patients with solid cancer and candidates to chemotherapy should be screened **(2C)**. Vote in favour: 98,1%.

Q2. Patients with solid cancer and HCV infection should be treated with DAAs **(2C)**. Vote in favour: 90,9%.

Q3. Patients treated with DAAs should be monitored by testing ALT and serum HCV-RNA level before the start of therapy, at the end of therapy and 12-week after the end of therapy for the evaluation of SVR. **(1B)**. Vote in favour: 88%.

Q4. All patients should be treated with DAAs for the times indicated according to viral genotypes and the stage of disease. After confirmation of the SVR, no further HCV-RNA controls are required **(1B)**. Vote in favour: 98,1%.

4.3. Future perspectives

Epidemiology data show that over 50% of all new cancers in the United States and Europe are diagnosed among people aged 50–75 years, the prevalence of HCV infection in this age group is estimated to be over 2% and many of these subjects have a chronic liver disease. Thus, screening for HCV infection in patients with solid cancers should be recommended, facilitated and therapy with DAAs considered as capable of eliminating the risk of HCV reactivation, hepatitis flare and to complete chemotherapy.

5. Hematology and hemopoietic cells transplant (HCT)

5.1. Epidemiology

In endemic areas as Italy, a 17.9% (16.6–19.2, 95%CI) prevalence of HCV infection in the lymphoma population has been described and a causative association between this infection and B cell non-Hodgkin lymphomas (nHL) has been reported [49]. As a further evidence of a causative role in lymphomagenesis, HCV-positive B cell indolent nHL can in some instances be successfully treated with antiviral therapy only [40–43,50,51] and successful HCV eradication seems to reduce the risk of subsequent lymphoma development [52]. HCV screening rate before lymphoma treatment is high (97.8%/86%) [53,54].

5.2. Clinical impact

Active HCV infection has often been considered as an exclusion criteria from trials testing anti-lymphoma treatments. However, in real world practice, its presence in diffuse large B cell lymphomas (DLBCL) is associated with higher incidence of treatment-related toxicities (grade 3–4), dose reductions and

(immune)-chemotherapy interruptions [47,48,53,54]. On the other hand, available data show that overall and progression free survival do not seem to be affected by HCV infection in DLBCL patients [49]. A faster progression to cirrhosis has been reported among HCV-positive patients undergoing HCT [31], particularly in presence of comorbidities such as hepatic iron overload [55]. Nonetheless, data from special subpopulations (i.e. HCV-positive patients undergoing HCT for HIV-related lymphomas) do not seem to confirm such trend [56].

HCVr incidence during lymphoproliferative diseases/HCT is currently poorly defined. Various medications have been associated with HCVr, in particular following rituximab and high dose steroids treatments [57–59]. HCVr is rarely fatal, in fact most cases show an indolent course [31], but fatal cholestatic hepatitis do occur [60]. In the only available prospective observational study, HCVr developed in 36% (18/50) [95% CI: 22–50] of patients treated for lymphoproliferative diseases, with flares in 44% of the cases (8/18; 47).

5.3. Treatment

Timing of HCV treatment (concomitant, sequential, on case by case criteria) in lymphoproliferative diseases patients (B cell nHL in particular) remains controversial because available data are still limited by sample size, mostly based on case series [61], and even expert opinions [23]. Some general indications however emerged: (1) a different approach between indolent and aggressive lymphoproliferative diseases (WHO 2016 criteria) should be considered; (2) HCV treatment should be offered to indolent B cell nHL patients not fulfilling the criteria for immediate immunochemotherapy beginning (marginal zone lymphoma in particular) [27,62–65]; (3) upfront chemo-free combination of DAAs and rituximab to treat HCV-associated indolent nHL with high tumor burden are attractive, but need prospective studies [66]; (4) HCV-RNA positive patients with DLBCL/rapidly progressive/symptomatic indolent lymphomas (progressive leukemic phase, bulky nodal or extranodal masses or splenomegaly, systemic symptoms), should be managed according to current hematological guidelines; DAAs treatment could either be concomitant [36] or delayed [66]. More data are needed to refine strategies, considering the disturbing, even if anecdotal, observations of early progression to aggressive lymphoma after DAAs [61].

DAAs-obtained HCV eradication not only prevents progression to cirrhosis and liver-disease related events, but also might hinder lymphoma relapse. Clearance of a postulated antigen-dependent low-grade clone may in fact eradicate the relapse trigger, especially in those B cell nHL showing histological evidence of evolution from lower grades [57]. Viral eradication may protect against immunochemotherapy-related side effects development [31], allowing to complete scheduled treatments without interruptions [57]. In patients with a limited life expectancy HCV treatment can reasonably be excluded [23].

As far as ***HCT*** (autologous and allogeneic) is concerned, considering that active HCV infection is not currently held as an absolute contraindication [67], and since this treatment is not considered a first line strategy in lymphoproliferative diseases, HCV management should be considered in the initial steps of evaluation according to the present guidelines. In case of HCV-positive donors, currently not excluded from donation if necessary, it seems reasonable to suggest that, if time allows, they should start antiviral therapy as soon as possible, with the aim to eliminate the infectious potential, ideally attaining undetectable HCV-RNA before hemopoietic cell harvest [67]. HCVr as the result of chemotherapy after successful SVR is to be considered highly unlikely [48].

Regular monitoring is suggested for HCV-infected patients undergoing chemotherapy, HCT, depleting antibodies and newly introduced drugs (i.e. lenalidomide, BCL2 and BK inhibitors). HCVr and flares can develop during the course of treatment, but usually occur weeks or months after immunosuppression withdrawal; accordingly further successive follow up surveillance is also suggested [31,68].

Questions

Q1. All candidates to HCT, chemo or immune-chemotherapy for lymphoproliferative diseases should be tested for HCV **(1B)**. Vote in favour: 100%.

Q2. HCV RNA positive patients with lymphoproliferative diseases should be treated for HCV infection with currently approved DAAs regiments. Antiviral therapy:

1) should be offered as *first line treatment* to patients with indolent B cell NHL not fulfilling the criteria for immediate start of immuno-chemotherapy **(1B)**. Vote in favour: 97,9%.
2) can be either *concomitant (if feasible) or delayed* in patients with rapidly progressive and symptomatic indolent lymphomas and those affected by others form of lymphoproliferative diseases including DLBCL who can undergo immuno-chemotherapy according to current guidelines for lymphoma **(1C)**. Vote in favour: 97,9%.

Q3. HCV-RNA positive patients should be regularly monitored during treatment with chemo- or immune-chemotherapy, before the initiation of chemotherapy, at 12-week intervals after initiation of cancer treatment and at the time of hepatitis flare. Further follow up surveillance after the end of the immunosuppressive treatment is also suggested **(1B)**. Vote in favour: 100%.

Q4. Monitoring should be continued up to demonstration of HCV eradication **(2C)**. Vote in favour: 100%.

5.4. Future perspectives

More data are needed to define the appropriate timing of HCV treatment among patients with DLBCL, rapidly progressive/symptomatic indolent lymphomas and other aggressive lymphoproliferative diseases. The rare but reported case of progression to aggressive lymphoma should be addressed. In patients with lymphoproliferative diseases HCV treatment should be acknowledged as a relevant management opportunity.

6. Coinfections

The strategy of treatment in HCV/HBV coinfection has been described in a specific document aimed to HBV.

7. Liver transplantation

7.1. Epidemiology

HCV infection represents the leading cause of death due to liver disease and the common indication to liver transplantation (LT) in the United States and Europe [69].

7.2. Clinical impact and background

In recipients who undergo LT with active HCV replication, hepatitis HCV recurrence in the graft is universal [70]. Liver fibrosis progression due to HCV recurrence in liver transplanted patients is faster as compared to immune-competent patients [71]. This implies that about 30% of HCV positive recipients developed graft cirrhosis five years after LT [72]. Severe HCV recurrence is responsible for the worse outcome in HCV-positive recipients than in patients undergoing LT for other indications [73]. The recent introduction of new potent and safe DAAs has dramatically changed the

scenario of HCV therapy in the context of LT. The vast majority of HCV positive patients with severe liver disease can now be treated successfully either pre- or post-LT [70,74]. Given their favorable profile, two different approaches can now be pursued:

- treating HCV infection before LT, while the patient is on the waiting list with the aim to prevent HCV recurrence in the graft, improve liver function to explore the possibility of patient delisting and facilitate post-LT management;
- treating HCV infection after LT, either soon afterwards to take advantage of the removal of the infected native liver and the consequently very low viral burden, or at the time of HCV recurrence, to prevent fibrosis progression.

7.3. Antiviral treatment before LT (strategy 1)

Besides the prevention of HCV recurrence, achievement of sustained viral response (SVR) with antivirals in HCV positive patients with decompensated cirrhosis has led, in some cases, to the improvement of liver synthetic function and/or to the reduction of portal hypertensive complications [75–78]. These goals should improve patient survival on the waiting list and in some cases, may also allow avoidance of LT [79]. However, it should be pointed out that the achievement of SVR could not prevent disease progression or liver-related mortality in the sickest patients, particularly those who present severe hepatic insufficiency and portal hypertension [80–82]. To date it is not completely clear which can be considered the "point of no return" dividing patients with decompensated cirrhosis who will really benefit from the achievement of SVR. It is currently accepted and recommended that patients waiting for liver transplant with MELD score >18–20 will benefit from liver transplantation first and antiviral treatment started as soon as possible after liver transplantation [83]. A very challenging issue concerns patients with SVR and partial improvement of MELD who could, paradoxically, have a reduced priority access to LT ("purgatory MELD") [83]. Moreover, the failure to achieve SVR, observed more frequently in patients with decompensated liver cirrhosis, could determine the selection of HCV resistant variants making retreatment strategies difficult, particularly in HCV genotype 3 infected patients [84].

Question for strategy 1 (* subsections were voted overall).

Q1. Who should or should be not treated before LT?

Q1.1a Patients with hepatocellular carcinoma (HCC) and compensated cirrhosis should receive antiviral therapy if the waiting time for LT is expected to be over 3 months **(1C)**.

Q1.1b. Patients with or without HCC with decompensated liver cirrhosis should be considered for antiviral therapy if they have MELD score $\leq$20 and are without refractory portal hypertensive symptoms or other conditions requiring more immediate LT **(2C)**.

Q1.1c. Antiviral therapy before LT should be considered on individual bases in wait-listed patients with or without HCC and decompensated cirrhosis with intermediate MELD scores (21–29) and/or low MELD scores but having refractory portal hypertensive complications (i.e. MELD exceptions) **(2B)**.

Q1.1. Patients with decompensated liver cirrhosis with or without HCC and MELD $\geq$30 or those who are expected to receive the highest priority for LT should receive antiviral therapy after LT **(2C)**.

Vote in favour: 95,7%*.

Q2. How should be treated patients in the waiting list?

Q2.1a The combination of HCV polymerase and NS5A or the combination of NS5A and NS3 protease inhibitors can be used **(1A)**.

Q2.1b NS5A plus NS3 protease inhibitors combination should be avoided in Child–Pugh class B and C **(1A)**.

Q2.1c In patients with creatinine clearance <30 ml/min/1.73 m^2 sofosbuvir cannot be used. Antiviral strategies combining HCV NS3 and NS5A protease inhibitors should be considered with the exception of those in Child Pugh class B and C **(1A)**.

Q2.1d. The effective prevention of post LT HCV recurrence requires a period of DAAs induced virological suppression of at least 30 days prior LT **(1B)**.

Q2.1e If the waiting time for liver transplantation is expected to be not long enough to reach this goal, the option to start antiviral therapy after liver transplant should be preferred **(2B)**.

Q2.1f. In patients who are on antiviral treatment with DAAs but have not reached a virological suppression for at least 30 days, liver transplantation should not be denied and antiviral treatment should be re-started after liver transplant **(2B)**.

Vote in favour: 96,4%*.

7.4. Antiviral treatment after LT (strategy 2)

Antiviral treatment with new DAAs in recurrent HCV related hepatitis after LT allows to obtain SVR in more than 95% recipients [75]. This result was independent from the degree of graft fibrosis until a stage of compensated cirrhosis and from the presence of fibrosing cholestatic hepatitis [85]. Recent reports clearly indicate that the achievement of SVR is associated with an improvement of patients and graft survival after LT [86]. It should be anticipated that the progression to decompensated cirrhosis will be a rare event in the DAAs era, however, some recipients under care currently present this condition. This raises the question whether it could be sufficient to use antiviral therapy with DAA as a single strategy, expecting a significant clinical improvement in all treated patients, or if could be better to evaluate the candidacy of these patients for re-transplantation. It should be pointed out that SVR at week 12 after therapy (SVR 12) is still suboptimal in DAA-treated patients with decompensated HCV related liver cirrhosis and that the clinical benefit of antiviral treatment is significantly reduced by the presence at baseline of ascites, hepatic encephalopathy and low albumin levels [87]. Since the baseline negative predictive factors of clinical improvement after antiviral therapy are often present in patients with decompensated cirrhosis due to HCV recurrence, the potential candidacy to re-transplantation should be considered firstly.

Question for strategy 2

Q1. Who should be treated after LT?

Q1.2a All HCV-RNA positive recipients should be treated as early as possible after LT. Patients who experienced fibrosing cholestatic variant of HCV recurrence should take higher priority **(1B).**

Q1.2 b. In patients with decompensated graft cirrhosis due to HCV recurrence, the first option to consider is re-transplantation. Antiviral therapy should only be offered as a first option to patients with contraindications for re-transplantation whose advanced liver disease represents their main risk of death **(1B)**.

Vote in favour: 96,2%*.

Q2. How patients should be treated?

Q2.2a The choice of drug combination and treatment duration should be decided on the bases of stage of liver disease, HCV genotype, renal function and DDIs **(1A)**.

Q2.2b. Longer (24 weeks) duration of treatment should be considered in patients intolerant or who have contraindications for ribavirin use **(1B).**

Vote in favour: 98%*.

Q3. Who should be monitored and how?

Q3.1. The efficacy of antiviral treatment must be done by serum HCV-RNA measurement using high-sensitivity real-time PCR. Patients should be tested for HCV RNA at least 12 and 24 weeks after the completion of treatment to determine the achievement of SVR **(1A)**.

Q3.2. In patients who fail to achieve SVR, resistance testing in HCV NS3, NS5A and NS5B regions is mandatory before to decide the retreatment scheme to adopt **(1A)**.

Q3.3. Serum levels of immune-suppressive drugs should be checked frequently during and at the end of antiviral treatment while serum levels of hemoglobin and creatinine clearance should be assessed to evaluate the impact of ribavirin **(1B)**.

Vote in favour: 100%*.

7.5. Future perspectives

Despite the high efficacy and safety of new DAAs combinations, there are still several issues that should be clarified: (1) the minimum duration of pre-LT HCV RNA negativity necessary to prevent HCV recurrence; (2) in patients with HCC, the possible influence of antiviral therapy on the rate of HCC recurrence after LT, particularly in patients transplanted outside Milan criteria after effective tumor down staging; (3) the clear identification of the "point of no return", beyond which the achievement of SVR does not yield substantial clinical improvement to allow patient delisting; (4) how to consider patients who achieved SVR and "purgatory MELD" condition. It is still unclear if these patients should receive any priority to LT as compared to HCV negatives with the same MELD score.

A further area of great interest is to evaluate the feasibility and safety of using anti-HCV-positive or HCV RNA positive donors in anti-HCV-negative recipients [88]. Theoretically, new DAAs will allow to cure HCV infection easily in all these recipients, but besides clinical issues, this scenario will imply legal and ethical considerations [89].

In the post-LT setting, avoidance of ribavirin is desirable given the reduction in renal perfusion due to the use of calcineurin inhibitors and reduced hemoglobin levels. Studies aimed to evaluate the efficacy of ribavirin-free combinations to treat relapsers or HCV genotype 3 infected recipients are needed. While efficacy data are expected to be similar to non-LT populations, the combinations of grazoprevir/elbasvir and glecaprevir/pibrentasvir should be studied more extensively in patients with renal impairment after LT and, including the combination of sofosbuvir/velpatasvir/voxilaprevir, in those who failed a previous DAA regimen.

8. Solid organ tranplants (SOTs)

8.1. Epidemiology

Today prevalence of HCV infection in non-renal SOT candidates appears to approximate that of the background population. In older studies, HCV infection in cardiac transplant recipients was initially reported to be as high as 11–18% and dropped from 28% to 4.2% in transplant recipients transplanted before and after 1990 [89–95] (Table 3).

8.2. Clinical impact

The impact of HCV infection on the outcome of non-hepatic SOT has been studied most extensively in renal transplant recipients.

Table 3
HCV prevalence in pre and post transplant heart-transplant (HTx) recipients (*anti-HCV+, 6% HCV-RNA*).

	HCV prevalence	
	Pre-HTx	Post-HTx
Cadranel, [127]	–	18.0%
Zein, 1994	–	7.0%
Lunel, 1995	–	10.4%
Preiksaitis, [97]	2.3%	10.2%
Fagiuoli, [94]	0.6%	8.0%
Cotler, [91]	1.9%	–
Lunel, [92]	1.7%	10.6%
Fagiuoli, [98]	2.7%	9.4%
Gasink, [90]	12.5%*	–

Indeed, just a few long-term studies have explored the outcome of heart, lung, small bowel or pancreas recipients.

8.3. Heart

Contradictory evidences are available likely due to short term follow up and relatively small number of patients in the studied cohorts [92,96,97]. In two small series, HCV infection did not impact patients and graft survival on the short term [98,99]. However, a recent retrospective analysis of the UNOS database (1991–2014) demonstrated that HCV positive recipients presented a worse outcome (4 years follow up) as compared to HCV negative recipients, since late renal and liver dysfunction occured more frequently in positive recipients [100]. Different mechanisms have been proposed to explain reduced survival and increase morbidity in HCV-infected cardiac recipients, such as earlier onset of cirrhosis and its complication, and accelerated coronary heart disease [101] (Table 4).

8.4. Lung

In two small cohorts from single centre experiences and in a retrospective analysis of the UNOS database, the 5-year survival was similar in HCV positive and negative recipients [102–104]. However, the results of these studies were limited by the lack of data on HCV-RNA status. By contrast, a recent retrospective analysis from scientific registry of transplant recipient (1995–2011) have shown a moderate mortality increase in HCV positive recipients [105]. Despite the limited data, HCV infection is still a relative contraindication to lung transplantation for the International Society for Heart and Lung Transplantation (2015). It is suggested that transplant can be considered in patients "without evidence of cirrhosis" and on "appropriate therapy" and that such patients should be managed in centres with expertise in viral hepatitis.

8.5. Pancreas

Available data on pancreas and pancreas-kidney are poor, but these patients appear to be at higher risk of graft dysfunction and morbidity (sepsis, higher risk of renal dysfunction with proteinuria

Table 4
Prevalence of HCV infection and chronic liver disease in heart transplant recipients.

	HCV prevalence	CLD	Cirrhosis	Liver failure	Mean follow-up years
Cadranel, [127]	18%	63%	–		5
Zein, 1994	7%	–	–		–
Lunel, 1995	10.4%	62%	0%	0	5
Fagiuoli, [94]	8%	66%	15%	15%	5
Lunel, [92]	10.6%	100%	–	0	8
Fagiuoli, [98]	12%	58%	28%	7%	8

and poor glycemic control) [106]. No data exists regarding survival in small bowel transplant recipients with HCV infection.

In the pre-DAA era, IFN-based therapy was contraindicated in patients with end-stage heart failure, due to the increased risk of arrhythmia and cardiotoxicity. Furthermore, the risk of ribavirin-related anaemia was bound to worsen any underlying cardiac ischemia. Additionally, the results of IFN-based regimens in small series of patients were contradictory [107,108].

The advent of DAAs has dramatically changed the clinical scenario. However, limited experience on their use in patients with SOT is available. DAAs have demonstrated to be extremely effective and safe in few case reports in the pre- and post-heart transplant setting, but safety in patients with congestive heart failure remains very inadequate [109,110]. No evidence is reported on the use of DAAs in lung or pancreas transplant recipients. However, the experience from kidney transplant studies recommends early therapy for HCV infection. Patients should be referred to expert centres and DDIs carefully evaluated.

Finally, nowadays the shortage of organs for transplantation is a major impediment and the use of HCV-positive donors may represent a potential approach to safely expand the donor pool in the DAA era.

Questions

Q1. All SOT recipients should be tested for anti-HCV markers, including HCV RNA, genotype and full assessment of liver dysfunction. Liver biopsy or non-invasive evaluation of liver fibrosis (elastometry or serum markers diagnosis) is recommended to confirm or to rule out the presence of cirrhosis **(1A)**. Vote in favour: 100%.

Q2 (Recipients). The decision to perform anti-HCV therapy pre- or post-transplantation should be discussed at the individual level **(2C)**.

Q2a. If adopting a pre-transplant antiviral treatment strategy all patients should be treated regardless of fibrosis stage **(1B)**.

After-transplant all new and "long-term" SOT recipients should be treated after with DAAs regardless of the fibrosis stage (DDIs with immunosuppressive drug must be taken into account) **(1B)**. Vote in favour: 93,2%*.

Q2. (Donors). HCV positive grafts should be utilized in HCV-positive ("viremic") recipients. Grafting of HCV-viremic organs into non-viremic recipients should only be conducted under approved study protocols **(1C)**. Vote in favour 93.6%.

8.6. Future perspectives

The use of HCV-positive organ donors in negative recipients is an intriguing possibility. Indeed, with the availability of DAAs between 2015 and 2016, the allocation of HCV-positive organs into HCV-negative recipients tripled in liver transplant and doubled in kidney transplants. This trend has also been observed in thoracic transplants [107]. Although it still occurs in small numbers, this option is an emerging trend due to different reasons: (1) the widespread use of DAAs has increased the number of non-viremic candidates; (2) the increasing confidence in the success of curing HCV after transplant; (3) the recent experience in renal transplant, confirming the excellent results of a pre-emptive treatment with DAA in case of use of positive HCV donors in negative recipients [108,109].

9. Nephrology

9.1. Epidemiology

Prevalence of HCV infection among dialysis patients and renal transplant recipients has historically been high as a consequence of nosocomial HCV transmission by repeated haemodialysis, blood transfusions and HCV-infected kidney grafts transplantation. Due to improvements of medical standards, prevalence of HCV infection in the dialysis population decreased from 10 to 13% in the early 90s, to approximately 7–8% in the early 2000s in developed countries, with an estimated 0.2% per year transmission. Conversely, in developing countries, up to 80% prevalence and 15% yearly transmission rate have been reported in single centre studies [110,111].

9.2. Clinical impact

HCV infection is associated with increased morbidity and mortality both in the dialysis and the post-transplant settings, where HCV is an established risk factor for graft loss [111–113]. Moreover, HCV infection adds further non-kidney related mortality, being associated with increased liver-related complications, diabetes and cardiovascular events, as well as cancer-related deaths [114–117].

Chronic HCV infection in dialysis patients is often characterized by persistently normal aminotransferase (ALT) values, since repeated haemodialysis reduce ALT levels. Consequently, ALT are not reliable markers of liver disease activity and progressive liver disease has been demonstrated in patients with persistently normal ALT. In renal transplant recipients, HCV infection is associated with accelerated liver disease progression and kidney graft impairment [112].

All dialysis patients and renal transplantation candidates should be screened for this infection by anti-HCV testing. Although currently available assays provide optimal sensitivity, reduced antibody response to HCV antigens has been reported in dialysis patients [116]. HCV RNA assessment should thus be performed in all patients candidates to transplantation, so as the poorer prognosis of kidney transplant recipients with hepatitis C. Due to the persistent risk of HCV transmission, HCV screening in haemodialysis patients should be regularly repeated overtime.

Availability of DAAs has changed HCV treatment in dialysis and renal transplant recipients, providing increased SVR rates and safer treatment options among those with prior contraindications to IFN-based regimens. All viremic HCV dialysis patients and renal transplant recipients should be considered for antiviral therapy: in dialysis patients, treatment options are currently available for all HCV genotypes. As stated above, sofosbuvir-based regimens are currently not recommended if eGFR is <30 ml/min, although they have been used in real-life settings [27].

In renal transplant recipients, antiviral treatment should be performed after renal function stabilization. A randomized trial demonstrated optimal efficacy and safety of sofosbuvir/ledipasvir in HCV genotype 1 and 4 patients, and sofosbuvir/velpatasvir or sofosbuvir + daclatasvir combinations are approved in the post-transplant, although data are still limited [117]. DDIs with patient's concomitant medications should be carefully assessed. The decision to treat before or after transplant should be discussed at an individual level, according to local drug availability, patient comorbidities and access to waitlist for renal transplant.

HCV dialysis patients should be referred for specialist care to stage liver disease and antiviral treatment evaluation. Eligibility to antiviral therapy should be regularly reassessed in patients without current treatment options. Monitoring of ALT values and liver function tests should be regularly performed in HCV dialysis patients and renal transplant recipients not receiving antiviral treatment.

Questions

Q1. All dialysis and renal transplant recipients should be screened for HCV infection **(1A)**. Vote in favour: 100%.

Q2. All HCV dialysis and and kidney transplant recipients should be evaluated for antiviral treatment **(1B)**.

Q2a. The decision to perform anti-HCV therapy pre- or post-renal transplantation should be discussed at the individual level; patients should be referred to expert centers to manage access to antiviral treatment and/or renal transplant **(2C)**.

Q2b. All HCV renal transplant recipients should receive antiviral treatment **(1B)**. Vote in favour: 100%*.

Q3. Monitoring of liver function tests should be regularly performed in HCV dialysis patients and renal transplant recipients not receiving antiviral treatment **(1C)**. Vote in favour: 100%.

9.3. Future directions and research priorities

Large scale treatment of HCV infection with DAA-based regimens is expected to deeply affect HCV prevalence worldwide in the next decades. The possibility to extensively treat dialysis patients and renal transplant recipients will lead to new scenarios: access to HCV-positive kidney graft pool in order to reduce time on the waiting list could be systematically pursed considering the availability of antiviral treatments in the post-transplant phase. This strategy has already been applied to HCV-positive recipients, and future developments could also extend it to HCV-negative renal transplant candidates [118].

10. Rheumatology

10.1. Epidemiology

Prevalence of HCV infection among patients with rheumatic diseases is poorly known. Although epidemiological studies are limited to specific population or geographic areas, prevalence seems to be slight higher than, or at least comparable to, that of the general population [119,120]. These patients may need long term and often multiple immunosuppressive therapies to obtain clinical remission. Immunosuppressive treatments place them at risk of viral reactivation.

10.2. Clinical impact

HCVr seems to be a rare event. Serum HCV RNA may increase during immunosuppressive therapies, however without clinically significant hepatitis [121]. Immunosuppressive therapies do not seem to have a detrimental effect on the course of HCV infection. Experiences on the concomitant treatment with both immunosuppressive drugs and DAA are limited [122].

Questions

Q1. All rheumatologic patients should be tested for anti-HCV (plus HCV RNA if positive) before starting immunosuppressive therapy **(1C)**. Vote in favour: 97,7%.

Q2. The detection of a chronic hepatitis C should promptly lead to treatment with DAAs. Careful check of DDIs between immunosuppressive regimens and HCV drugs is recommended **(1C)**. Vote in favour: 97,6%.

Q3. All untreated patients should be monitored with liver test every 3-6 months. HCV RNA monitoring has no clinical utility **(1C)**. Vote in favour 85%.

Q4. No modifications of the standard hepatological follow up is needed in HCV patients after the end of immunosuppressive therapy **(1A)**. Vote in favour: 97,8%.

10.3. Future perspectives

The therapeutic scenario for rheumatic disease is rapidly evolving and new drugs with potential great efficacy will be available in the next future. The effects of these new drugs on the course of chronic viral hepatitis are unknown.

11. Gastroenterology

11.1. Epidemiology

Ulcerative colitis and Crohn's disease (IBD) mainly affect young subjects, reaching their peaks in the third decade of life [123]. As a consequence, the burden of concurrent chronic viral hepatitis in Italian IBD patients is limited by the low prevalence of HCV infection among young subjects.

11.2. Clinical impact

There is general consensus about the fact that immunosuppressants or biologics used in IBD do not seem to have a significant effect on the course of HCV infection, because the risk of HCVr during these immunosuppressive therapies appears to be very low and they do not influence the progression of chronic liver disease [124,125]. However, although these drugs do not seem to have a detrimental effect on the course of HCV infection, the awareness of a concomitant chronic hepatitis C is important due to the potential risk of worsening liver function and to better discriminate the alterations of liver function tests as due to the use of drugs with potential hepatotoxicity (azathioprine, methotrexate, biologics) or HCV infection [126].

Questions

Q1. All IBD patients to be treated with immunosuppressants or biologics should be tested for anti-HCV (HCV RNA if positive). The ideal time to screen is at the diagnosis of the disease, regardless of its severity at onset **(1B).** Vote in favour: 95,1%.

Q2. The detection of a chronic hepatitis C should lead to treatment with the new DAAs. Careful check of DDIs with immunosuppressive regimens is recommended **(1A)**. Vote in favour: 100%.

11.3. Future perspectives

The therapeutic scenario for IBD is rapidly evolving. Over the past 20 years, drug research has focused on the development of large-molecule biologics, including anti-TNF-α monoclonal antibodies and, more recently, antibodies with different targets (such as vedolizumab, ustekinumab, and others). Furthermore, new orally administered small molecule drugs with potential great efficacy will be available in the next future. The effect of these new drugs on the course of chronic viral hepatitis is unknown and this reinforces the indication to screen and treat viral hepatitis in these patients.

Conflict of interest

Estensor	Pharmaceutical company	Relationship
Emanuele Angelucci	Novartis	Chair Steering committee, Advisory board, Invited speaker
	Celgene	Chair DSMC, advisory
	Shire	Advisory board
	Roche S.p.A.	Advisory board
	Jazz Pharmaceuticals	Advisory board
Marco Astegiano	None	None
Chiara Baratelli	None	None
Luigi Biancone	Astellas Pharma S.p.A.	Advisory board
Paolo Bironzo	Bristol-Myers Squibb S.r.l.	Honoraria
	MSD Italia S.r.l.	Research grant
Giuseppina Brancaccio	AbbVie s.r.l., Gilead Sciences S.r.l.	Speaker
Maurizia Rossana Brunetto	AbbVie s.r.l., Gilead Sciences S.r.l., MSD Italia S.r.l.	Advisory board

	AbbVie s.r.l., Bristol-Myers Squibb S.r.l., Gilead Sciences S.r.l., Janssen, MSD Italia S.r.l.	Speakers bureau
	AbbVie s.r.l., Bristol-Myers Squibb S.r.l., MSD Italia S.r.l.	Research Grants
Raffaele Bruno	AbbVie s.r.l., Bristol-Myers Squibb S.r.l., Gilead Sciences S.r.l., MSD Italia S.r.l.	Advisory Board, Speaker
Patrizia Burra	Novartis	
	Astellas	
	Grifols	Letture
	Kedrion S.p.A.	Congress
	Sandoz	Advisory Board
	Gilead Sciences S.r.l.	
	Alfa Wassermann	
Maria Giuseppina Cabras	None	None
Paolo Caraceni	Grifols SA	Advisory board
	Kedrion S.p.A.	Speaking Bureau
	Octapharma S.p.A.	Speaking Bureau and Research Grant
Claudia Chialà	None	None
Maria Grazia Clemente	None	None
Agostino Colli	None	None
Stefano Cusinato	None	None
Bruno Daniele	Bayer S.p.A.	Advisory Board, Speakers bureau
	Eisai	Advisory Board
	Bristol-Myers Squibb S.r.l.	Advisory Board, Speakers bureau
	MSD Italia S.r.l.	Advisory Board
	IPSEN	Advisory Board
	Lilly	Advisory Board
Elisabetta De Gasperi	AbbVie s.r.l., Gilead Sciences S.r.l., MSD Italia S.r.l.	Speaking and Teaching, Travel Grant
Massimo Di Maio	None	None
Vito Di Marco	None	None
Maria Chiara Ditto	Lilly	Consulting Fees
Stefano Fagiuoli	MSD Italia S.r.l., AbbVie s.r.l., Gilead Sciences S.r.l., Bristol-Myers Squibb S.r.l., Novartis, Kedrion S.p.A., Bayer S.p.A.	Speaker's Bureau e Advisory Board
Clodoveo Ferri	None	None
Giovanni Battista Gaeta	AbbVie s.r.l.	Advisory Boards, Speaker fees, Research support
	Merck	Advisory Boards, Speaker fees, Meeting organization
	Gilead Sciences S.r.l.	Advisory boards, Speaker fees
	Bristol-Myers Squibb S.r.l.	Speaker fees
	BioTest	Speaker fee
Stefano Ginanni Corradini	None	None
Paolo Antonio Grossi	None	None
Barbara Imperatrice	None	None
Pietro Lampertico	Bristol-Myers Squibb S.r.l., Roche, Gilead Sciences S.r.l., GlaxoSmithKline, MSD Italia S.r.l.	Advisory boards and speakers bureau
Alfredo Marzano	Gilead Sciences S.r.l., Bristol-Myers Squibb S.r.l, Kedrion S.p.a.	Advisory boards and speakers bureau
Fabio Salvatore Macaluso	None	None
Salvatore Madonia	None	None
Massimo Marignani	AbbVie s.r.l., Bristol-Myers Squibb S.r.l., Dicofarm&AGPharma, Bayer S.p.A.	Advisory board, consulting fees, economical support for meeting organization
Chiara Mazzarelli	Bristol-Myers Squibb S.r.l.	Travel Grant
Alberto Mella	CREO Educational SRL	Speaker bureau: "MANAGEMENT DELL'URICEMIA NELLE NEFROLOGIE: RISULTATI DI UNA SURVEY PILOTA PIEMONTESE"
Roberto Minutolo	AbbVie s.r.l.	Advisory boards, speakers bureau
Gabriele Missale	None	None
Ambrogio Orlando	None	None
Simone Parisi	Celgene	Advisory board
	Janssen	Advisory board
	Novartis	Advisory board
	Sanofi	Advisory board
Luisa Pasulo	AbbVie s.r.l.	Advisory boards
Massimo Puoti	AbbVie s.r.l., MSD, Gilead Sciences S.r.l., Beckman Coulter, ViiV	Speaker in own events e/o in eventi formativi interni e/o grants di ricerca e travel grants e/o membro di advisory boards non permanenti
Giovanni Raimondo	AbbVie s.r.l., Bristol-Myers Squibb S.r.l., Gilead Sciences S.r.l., MSD	Advisory boards, consulting fees, research grants, speakers bureau, economical support for meeting organization
Maria Rendina	AbbVie s.r.l., Gilead Sciences S.r.l., MSD Italia S.r.l., Bristol-Myers Squibb S.r.l., Kedrion S.p.A., Biotest Italia S.r.l.	Advisory board and speaker bureau
Davide Ribaldone	None	None
Giuseppe Rossi	Roche, Janssen, Celgene, Amgen, Gilead Sciences S.r.l., Sanofi, AbbVie s.r.l., Novartis, Jazz Pharmaceuticals	Advisory boards
Piercarlo Sarzi Puttini	None	None
Tommaso Stroffolini	None	None
Pierluigi Toniutto	AbbVie s.r.l.	Advisory Board, Speaker Bureau
	MSD Italia S.r.l.	Advisory Board
	Gilead Sciences S.r.l.	Speaker Bureau
	Novartis	Speaker Bureau
Alessandra Tucci	None	None
Pietro Vajro	None	None
Mauro Viganò	Bristol-Myers Squibb S.r.l., Fujirebio Italia S.r.l., Gilead Sciences S.r.l., Roche	Consultant/Advisor/ Sponsored Lectures
Riccardo Volpes	None	None
Anna Linda Zignego	AbbVie s.r.l., Gilead Sciences S.r.l., Bristol-Myers Squibb S.r.l., MSD Italia S.r.l.	Advisory boards, consulting fees, speakers bureau, economical support for meeting organization

Reviewer/jury	Pharmaceutical company	Relationship
Stefano Bonora	Merck, Viiv, Janssen, AbbVie s.r.l., Gilead Sciences S.r.l., Bristol-Myers Squibb S.r.l.	Advisory boards, speaker fees
Enrico Brignardello	None	None
Alessandro Busca	Gilead Sciences S.r.l., MSD Italia S.r.l. Pfizer Novartis	Advisory Board Speaker

Giuseppe Cariti	None	None
Federica Cavallo	None	None
Massimiliano Conforti	None	None
Marta Coscia	Janssen	Research grant
	Gilead Sciences S.r.l.	Advisory Board
	AbbVie s.r.l.	Advisory Board
	Karyopharm	Research grant
Antonio Craxì	AbbVie s.r.l.	Scientific Advisorship, Lecturer, Research Grant
	MSD Italia S.r.l.	
	Gilead Sciences S.r.l.	
	Bristol-Myers Squibb S.r.l.	
Daniele Curci	None	None
Stefano Cusinato	None	None
Rossella Della Valle	None	None
Massimo Di Maio	Bristol Myers Squibb, Merck Sharp & Dohme, Janssen, AstraZeneca	Advisory boards, consulting fees
	Astellas, AstraZeneca	Economical support for meeting organization
Enrico Fusaro	None	None
Aldo Giacardi	None	None
Luisa Giaccone	Jazz Pharmaceuticals	Speakers bureau
Marco Lagget	None	None
Daniela Libertucci	None	None
Giuseppe Montrucchio	None	None
Ambrogio Orlando	None	None
Lorella Orsucci	AbbVie s.r.l., Janssen, Gilead Sciences S.r.l.	Advisory boards, speakers bureau, economical support for meeting organization
Carla Pasquina	None	None
Angelo Pera	None	None
Clara Lisa Peroni	None	None
Mario Pirisi	AbbVie s.r.l., Alfasigma S.p.A., Bayer S.p.A., Gilead Sciences S.r.l., MSD Italia S.r.l., Bristol-Myers Squibb S.r.l.	Speaker's Bureau, Advisory Board
Patrizia Racca	None	None
Franco Riccardini	None	None
Mario Rizzetto	None	None
Mauro Salizzoni	None	None
Mario Salomone	None	None
Giorgio Maria Saracco	Gilead Sciences S.r.l.	Advisory board, economical support for meeting organization
	AbbVie s.r.l.	
	MSD Italia S.r.l.	
Piercarlo Sarzi Puttini	None	None
Luca Scaglione	None	None
Paolo Solidoro	None	None
Giorgio Verme	None	None
Giuliano Torre	AbbVie s.r.l.	Consulting Fees
Rita Tozzi	None	None
Umberto Vitolo	None	None

Appendix A.

Alfredo Marzano. *Division of Gastroenterology, San Giovanni Battista Hospital, University of Torino* **(Project coordinator)**

Emanuele Angelucci. *Haematology and Transplant Center, San Martino Hospital, Genova*

Marco Astegiano. *Division of Gastroenterology, San Giovanni Battista Hospital, University of Torino*

Chiara Baratelli. *Department of Oncology, Mauriziano Hospital, Torino*

Luigi Biancone. *Division of Nephrology Dialysis Transplantation, San Giovanni Battista Hospital, Torino*

Paolo Bironzo. *Department of Oncology, San Luigi Gonzaga Hospital, Orbassano, University of Torino*

Giuseppina Brancaccio. *Infectious Disease, University of Padua and University of Campania, Napoli*

Maurizia Rossana Brunetto. *Internal Medicine, Department of Clinical and Experimental Medicine, University of Pisa*

Raffaele Bruno. *Department of Infectious disease, IRCCS San Matteo, University of Pavia*

Patrizia Burra. *Multivisceral Transplant Unit, Gastroenterology Department of Surgery, Oncology and Gastroenterology, University Hospital, Padova*

Maria Giuseppina Cabras. *Department of Haematology, Hospital Businco, Cagliari*

Paolo Caraceni. *Department of Medical and Surgical Sciences, University of Bologna*

Claudia Chialà. *Division of Gastroenterology, San Giovanni Battista Hospital, University of Torino*

Maria Grazia Clemente. *Pediatric Clinic, Department of Clinical and Experimental Medicine, University of Sassari*

Agostino Colli. *Internal Medicine Unit "A, Manzoni" Hospital, Lecco (Methodology and President of the Jury)*

Bruno Daniele. *Medical Oncology Unit, G. Rummo Hospital , Benevento*

Elisabetta De Gasperi. *CRC Ä.M. e A. MigliavaccaC̈enter for Liver Diseases, Division of Gastroenterology and Hepatology, IRCCS Ca' Granda Ospedale Maggiore Policlinico, University of Milano*

Vito Di Marco. *Sezione di Gastroenterologia e Epatologia, Dipartimento Biomedico di Medicina Interna e Specialistica, University of Palermo*

Maria Chiara Ditto. *Rheumatology, Città della Salute e della Scienza di Torino, San Giovanni Battista Hospital, Torino*

Stefano Fagiuoli. *Gastroenterology Hepatology and Transplantology and Department of Medicine and Transplantation - Papa Giovanni XXIII Hospital - Bergamo*

Clodoveo Ferri. *Rheumatology Unit, Azienda Policlinico di Modena, University of Modena e Reggio Emilia*

Giovanni Battista Gaeta. *Infectious Diseases, Campania University L̈uigi Vanvitelli,·NapoliStefano Ginanni Corradini. Liver Transplant Unit, Department of Clinical Medicine, Sapienza University of Roma*

Paolo Antonio Grossi. *Department of Transplantation and Infectious and Tropical Diseases Unit, University Hospital "ASST Sette Laghi", Varese*

Barbara Imperatrice. *Digestive and Liver Disease Department, AUO S.Andrea Roma and Division of Gastroenterology, San Giovanni Battista Hospital, University of Torino*

Pietro Lampertico. *CRC Ä.M. e A. MigliavaccaC̈enter for Liver Diseases, Division of Gastroenterology and Hepatology, IRCCS Ca' Granda Ospedale Maggiore Policlinico, University of Milano*

Fabio Salvatore Macaluso. *IBD Unit, "Villa Sofia-Cervello" Hospital, Palermo*

Salvatore Madonia. *Internal Medicine Department, V. Cervello Hospital, Palermo*

Massimo Marignani. *Digestive and Liver Disease Department, Liver Disease Section, AUO S.Andrea, Roma*

Chiara Mazzarelli. *Hepatology and Gastroenterology, ASST Grande Ospedale Metropolitano Niguarda, Milano*

Alberto Mella. *Division of Nephrology Dialysis Transplantation, San Giovanni Battista Hospital, University of Torino*

Gabriele Missale. *Unit of Infectious Disease and Hepatology - University Hospital of Parma*

Simone Parisi. *Rheumatology, Città della Salute e della Scienza di Torino, San Giovanni Battista Hospital, Torino*

Luisa Pasulo. *Gastroenterology Hepatology and Transplantology, Papa Giovanni XXIII Hospital, Bergamo*

Massimo Puoti. *Niguarda Hepatitis Center, Division of Infectious Diseases, ASST Grande Ospedale Metropolitano Niguarda, Milano*

Maria Rendina. *Gastroenterology and Digestive Endoscopy, Liver Outpatient Clinic - University Hospital Bari*

Davide Ribaldone. *Division of Gastroenterology, San Giovanni Battista Hospital, University of Torino*

Giuseppe Rossi. *Hematology Division and Oncology Department - Spedali Civili Brescia*

Pierluigi Toniutto. *Medical Liver Transplant Section, Department of Medical Sciences Experimental and Clinical, University of Udine, Udine*

Alessandra Tucci. *Division of Gastroenterology, San Giovanni Battista Hospital, University of Torino*

Pietro Vajro. *Department of Medicine, Surgery and Dentistry S̈cuola Medica Salernitana/̈Pediatrics Section, University of Salerno*

Mauro Viganò. *Hepatology Division, Ospedale San Giuseppe, University of Milano*

Riccardo Volpes. *Hepatology and Gastroenterology Unit ISMETT/IRCCS - Palermo*

Anna Linda Zignego. *Interdepartmental Hepatology Center MaSVE - Department of Experimental and Clinical Medicine - University of Florence*

Appendix B.

Project Coordinator: Alfredo Marzano (Torino)

Promoters and Scientific board: Maurizia Rossana Brunetto (Pisa), Raffaele Bruno (Pavia), Vito Di Marco (Palermo), Stefano Fagiuoli (Bergamo), Pietro Lampertico (Milano), Anna Linda Zignego (Firenze) *and the AISF governing board: Edoardo G. Giannini (Genova) (AISF Secretary), Luca Miele (Roma), Francesco Paolo Russo (Padova), Salvatore Petta (Palermo), Mauro Viganò (Milano)*

JURY

Stefano Bonora, *Torino, Infectious Diseases*
Enrico Brignardello, Torino, *Oncology.*
Alessandro Busca, Torino, Haematology
Giuseppe Cariti, Torino, *Infectious Diseases*
Federica Cavallo, Torino, Haematology
Massimiliano Conforti, EpaC Onlus, *Italian Liver Patient Association*
Marta Coscia, Torino, Haematology
Antonio Craxì, *Palermo, Hepatology, Palermo*
Daniele Curci, Torino, Nephrology nurse
Stefano Cusinato, *Borgomanero (Novara),* Nephrology
Massimo Di Maio, Torino, Oncology
Rossella Della Valle, Torino, Nephrology nurse
Enrico Fusaro, *Torino, Rheumatology*
Aldo Giacardi, *A.I.T.F. (Associazione Italiana Trapiantati di Fegato), Italian Liver Transplanted Patient Association*
Luisa Giaccone, Torino, Haematology
Marco Lagget, *Torino, Gastroenterology*
Daniela Libertucci, *Torino, Pneumology and Lung Transplantation*
Roberto Minutolo, Napoli, Nephrology
Giuseppe Montrucchio, *Torino, Internal Medicine*
Ambrogio Orlando, Palermo, Gastroenterology
Lorella Orsucci,*Torino, Haematology*
Carla Pasquina, *Torino, Gastroenterology nurse*
Angelo Pera, Torino, Gastroenterology
Clara Lisa Peroni, *Torino, Rheumatology*
Mario Pirisi, Novara, Internal Medicine
Patrizia Racca, Torino, Oncology
Franco Riccardini, Torino, Internal Medicine
Mario Rizzetto, *Torino, Hepatology*
Mauro Salizzoni, *Torino, Liver Transplantation Surgery*
Mario Salomone, *Chieri (TO), Nephrology*
Giorgio Maria Saracco, Torino, Gastroenterology
Luca Scaglione, *Torino, Internal Medicine*
Giuliano Torre, Roma, Pediatric Gastroenterology,
Rita Tozzi, *Torino, Gastroenterology nurse*
Umberto Vitolo, Torino, Haematology
Giorgio Verme, *Torino, Gastroenterology*

Appendix C.

Immunopathogenesis of HCV reactivation

Immune response to HCV infection can lead to self-limited infection with viral elimination and hepatocellular injury. The virus is known to be a strong interferon activator but it is also responsible for a series of mechanisms interfering with the intracellular interferon pathways, contributing to viral persistence during the early stage of infection [4–6].

In spite of effective activation of first line immune response, HCV infection results in a high rate of persistence, and even if the strength and breadth of HCV-specific T-cell response has been associated with virus clearance [5–7], the exact role of different immune mechanisms in viral control and immunopathogenesis have not thoroughly understood. Several mechanisms of impaired T and NK cell response have been described to explain viral persistence, comprising T-cell exhaustion, Treg expansion within the liver, and suboptimal activation of T-cells by liver antigen presenting cells in the hepatic suppressive environment [4].

In patients undergoing interferon treatment for chronic HCV infection, a higher level of CD8 cell response has been associated with sustained viral response (SVR) [6]. However the exact role of T-cell response in achieving viral clearance and SVR, either by peg-interferon or directly acting antivirals (DAAs) is currently not completely clear. Interestingly, DAAs have shown to be very effective also in transplant recipients with severe immunosuppression [7], questioning the true role of immune response in viral clearance in this setting.

Even if it has been clearly demonstrated that liver cell injury is immune mediated, and that T-cell response can control and clear HCV infection during the acute phase, the exact role of immune response in controlling viral replication during chronic infection has not been entirely clarified.

The immune pathogenesis of HCV reactivation seems to be similar to that of HBV. However, differences exist in virus biology and role of T- and B-cell mediated response in controlling the two infections. Indeed, even if immunosuppressive treatments in patients with chronic HCV infection may induce enhanced viral replication, transaminases increase develops in a limited number of cases, and severe hepatitis is a rare event.

Even if neutralizing antibodies do not provide control of HCV replication, and self-limited HCV infection does not lead to neutralizing protective antibodies, similarly to HBV immunosuppressive treatments targeting B-cells can be followed by enhanced HCV replication and severe hepatitis. However, in the great majority of cases these phenomena do not seem to affect overall survival [8]. In some studies the rate of hepatitis under pharmacological immunosuppression did not differ between HCV-positive and -negative patients [9]. Actually, in many reported cases it was not entirely clear if the transaminases flares were due to either HCV, drug-induced liver injury, or metastatic liver disease [10].

Recent reports have raised warning on the possible event of HBV reactivation among HCV-coinfected patients undergoing DAAs therapy [11], leading to transaminase flares and even fulminant hepatic failure. Whether viral-viral interference or immune-mediated mechanisms are responsible for this event it is not known. The combined effects of negative viral-viral interference loss, along with an enhanced immune mediated liver injury could influence reactivation. Moreover, HCV clearance could lead to the restoration and enhancement of cell mediated immune response as the result of a sudden drop of endogenous IFN-I levels, persistently elevated in chronic HCV infection. It has been shown that IFN-I can play a negative regulatory role on virus-specific T-cell response due to a counter regulatory action on the immune response that would be suddenly abolished [12]. However, these possible interpretations

of immunopathogenetic mechanisms responsible for the severe HBV reactivation described in this subgroup of patients deserve dedicated studies aimed at dissecting viral replication kinetics and antigen-specific cell mediated immune response.

References

[1] Sistema Nazionale per le Linee Guida Manuale metodologico. Milano: Zadig; 2013 http://www.medicinanarrativa.eu/wp-content/uploads/consensus_conference-1.pdf.
[2] Schünemann H, Brożek J, Guyatt G, Oxman A, editors. GRADE handbook. https://gdt.gradepro.org/app/handbook/handbook.html.
[3] Rehermann B, Nascimbeni M. Immunology of hepatitis B virus and hepatitis C virus infection. Nat Rev Immunol 2005;5:215–29.
[4] Missale G, Bertoni R, Lamonaca V, Valli A, Massari M, Mori C, et al. Different clinical behaviors of acute hepatitis C virus infection are associated with different vigor of the anti-viral cell-mediated immune response. J Clin Invest 1996;98:706–14.
[5] Pilli M, Zerbini A, Penna A, Orlandini A, Lukasiewicz E, Pawlotsky JM, et al. HCV-specific T-cell response in relation to viral kinetics and treatment outcome (DITTO-HCV project). Gastroenterology 2007;133:1132–43.
[6] D'Ambrosio R, Aghemo A, Rossetti V, Carrinola R, Colombo M. Sofosbuvir-based regimens for the treatment of hepatitis C virus in patients who underwent lung transplant: case series and review of the literature. Liver Int 2016;36:1585–9.
[7] Mahale P, Kontoyiannis DP, Chemaly RF, Jiang Y, Hwang JP, Davila M, et al. Acute exacerbation and reactivation of chronic hepatitis C virus infection in cancer patients. J Hepatol 2012;57:1177–85.
[8] Lee HL, Bae SH, Jang B, Hwang S, Yang H, Nam HC, et al. Reactivation of hepatitis C virus and its clinical outcomes in patients treated with systemic chemotherapy or immunosuppressive therapy. Gut Liver 2017;11:870–7.
[9] Morrow PK, Tarrand JJ, Taylor SH, Kau SW, Theriault RL, Hortobagyl GN, et al. Effects of chronic hepatitis C infection on the treatment of breast cancer patients. Ann Oncol 2010;21:1233–6.
[10] Holmes JA, Yu ML, Chung RT. Hepatitis B reactivation during or after direct acting antiviral therapy — implication for susceptible individuals. Expert Opin Drug Saf 2017;16:651–72.
[11] Teijaro JR, Ng C, Lee AM, Sullivan BM, Sheehan KC, Welch M, et al. Persistent LCMV infection is controlled by blockade of type I interferon signaling. Science 2013;340:207–11.
[12] Gower E, Estes C, Blach S, Razavi-Shearer K, Razavi H. Global epidemiology and genotype distribution of the hepatitis C virus infection. J Hepatol 2014;61:S45–57.
[13] Buonomo AR, Scotto R, Pinchera B, Coppola N, Monari C, Macera C, et al. Epidemiology and risk factors for hepatitis C virus genotypes in a high prevalence region in Italy. New Microbiol 2018;41:26–9.
[14] Gardini I, Bartoli M, Conforti M, Mennini FS, Marcellusi A, Lanati E. HCV — estimation of the number of diagnosed patients eligible to the new anti-HCV therapies in Italy. Eur Rev Med Pharmacol Sci 2016;20:S7–10.
[15] Andriulli A, Stroffolini T, Mariano A, Valvano MR, Grattagliano I, Ippolito AM, et al. Declining prevalence and increasing awareness of hepatitis C virus infection in Italy: a population-based survey. Eur J Int Med 2018;53(July):79–84.
[16] Morisco F, Loperto I, Stroffolini T, Lombardo FL, Cossiga V, Guarino M, et al. Prevalence and risk factors of HCV infection in a metropolitan area in southern Italy: tail of a cohort infected in past decades. J Med Virol 2017;89:291–7.
[17] Houghton M. The long and winding road leading to the identification of the hepatitis C virus. J Hepatol 2009;51:939–48.
[18] Kambara H, Fukuhara T, Shiokawa M, Ono C, Ohara Y, Kamitani W, et al. Establishment of a novel permissive cell line for the propagation of hepatitis C virus by expression of microRNA miR122. J Virol 2012;86:1382–93.
[19] Bukh J. The history of hepatitis C virus (HCV): basic research reveals unique features in phylogeny, evolution and the viral life cycle with new perspectives for epidemic control. J Hepatol 2016;65:S2–21.
[20] Ennishi D, Maeda Y, Niltsu N, Kojima M, Izutsu K, Takizawa J, et al. Hepatic toxicity and prognosis in hepatitis C virus-infected patients with diffuse large B-cell lymphoma treated with rituximab-containing chemotherapy regimens: a Japanese multicenter analysis. Blood 2010;116:5119–25.
[21] Park SH, Rehermann B. Immune response to HCV and other hepatitis viruses. Immunity 2014;40:13–24.
[22] Pileri P, Uematsu Y, Campagnoli S, Galli G, Falugi F, Petracca R, et al. Binding of hepatitis C virus to CD81. Science 1998;282:938–41.
[23] Ramos-Casals M, Zignego AL, Ferri C, Brito-Zeron P, Retamozo S, Casato M, et al. Evidence-based recommendations on the management of extrahepatic manifestations of chronic hepatitis C virus infection. J Hepatol 2017;66:1282–99.
[24] Syed GH, Khan M, Yang S, Siddiqui A. Hepatitis C Virus lipoviroparticles assemble in the endoplasmic reticulum (ER) and bud off from the ER to the Golgi compartment in COPII vesicles. J Virol 2017;91:1–17.
[25] Gastaldi G, Goossens N, Clement S, Negro F. Current level of evidence on causal association between hepatitis C virus and type 2 diabetes: a review. J Adv Res 2017;8:149–59.
[26] Ohata K, Hamasaki K, Toriyama K, Matsumoto K, Saeki A, Yanagi K, et al. Hepatic steatosis is a risk factor for hepatocellular carcinoma in patients with chronic hepatitis C virus infection. Cancer 2003;97:3036–43.
[27] EASL recommendations on treatment of hepatitis C 2016. J Hepatol 2017;66:153–94.
[28] European Association for the Study of the Liver. EASL-ALEH clinical practice guidelines: noninvasive tests for evaluation of liver disease severity and prognosis. J Hepatol 2015;63:237–64.
[29] Mahale P, Kontoyiannis DP, Chemaly RF, Jiang Y, Hwang JP, Davila M, et al. Acute exacerbation and reactivation of chronic hepatitis C virus infection in cancer patients. J Hepatol 2012;57:1177–85.
[30] Lee HL, Bae SH, Jang S, Yang H, Nam HC, Sung PS, et al. Reactivation of hepatitis C virus and its clinical outcomes in patients treated with systemic chemotherapy or immunosuppressive therapy. Gut Liver 2017;11:870–7.
[31] Torres HA, Shigle TL, Hammoudi N, Link JT, Samaniego F, Kaseb A, et al. The oncologic burden of hepatitis C virus infection: a clinical perspective. CA Cancer J Clin 2017;67:411–31.
[32] Sung PS, Bae SH, Jang JW, Song DS, Kim HY, Yoo SH, et al. Differences in the patterns and outcomes of enhanced viral replication between hepatitis C virus and hepatitis B virus in patients with hepatocellular carcinoma during transarterial chemolipiodolization. Korean J Hepatol 2011;17:299–306.
[33] Torres HA, Davila M. Reactivation of hepatitis B virus and hepatitis C virus in patients with cancer. Nat Rev Clin Oncol 2012;9:156–66.
[34] Foran JM. Hepatitis C in the rituximab era. Blood 2010;116:5081–2.
[35] Zuckerman E, Zuckerman T, Douer D, Qian D, Levine AM. Liver dysfunction in patients infected with hepatitis C virus undergoing chemotherapy for hematologic malignancies. Cancer 1998;83:1224–30.
[36] Persico M, Aglitti A, Caruso R, De Renzo A, Selleri C, Califano C, et al. Efficacy and safety of new direct antiviral agents in HCV infected patients with diffuse large B cell non-Hodgkin lymphoma. Hepatology 2018;67:48–55.
[37] Brancaccio G, Sorbo MC, Frigeri F, Rizzo V, Cantone M, Generini F, et al. Treatment of acute hepatitis C with ledipasvir and sofosbuvir in patients with hematological malignancies allows early re-start of chemotherapy. Clin Gastroenterol Hepatol 2018;16:977–8.
[38] Economides MP, Mahale P, Kyvemitakis A, Turturro F, Kantarjian H, Naing A, et al. Concomitant use of direct-acting antivirals and chemotherapy in hepatitis C virus-infected patients with cancer. Aliment Pharmacol Ther 2016;44:1235–41.
[39] Peveling-Oberhag J, Arcaini L, Hansmann ML, Zeuzem S. Hepatitis C-associated B-cell non Hodgkin lymphomas. Epidemiology, molecular signature and clinical management. J Hepatol 2013;59:169–77.
[40] Hermine O, Lefrere F, Bronowicki JP, Mariette X, Jondeau K, Eclache-Saudreau V, et al. Regression of splenic lymphoma with villous lymphocytes after treatment of hepatitis C virus infection. N Engl J Med 2002;347:89–94.
[41] Sultanik P, Klotz C, Brault P, Pol S, Mallet V. Regression of an HCV-associated disseminated marginal zone lymphoma under IFN-free antiviral treatment. Blood 2015;125:2446–7.
[42] Arcaini L, Besson C, Frigeni M, Fontaine H, Goldaniga M, Casato M, et al. Interferon- free antiviral treatment in B-cell lymphoproliferative disorders associated with hepatitis C virus infection. Blood 2016;1128:2527–32.
[43] Maciocia N, O' A, Brien, Ardeshna K. Remission of follicular lymphoma after treatment for hepatitis C virus infection. N Engl J Med 2016;375:1699–701.
[44] Hwang JP, Suarez-Almazor ME, Torres HA, Palla SL, Huang DS, Fisch MJ, et al. Hepatitis C virus screening in patients with cancer receiving chemotherapy. J Oncol Pract 2014;10:e167–74.
[45] Brasseur M, Heurguè-Berlot A, Barbe C, Brami C, Rev JB, Vella-Boucaud J, et al. Prevalence of hepatitis B and C and sensibility of a selective screening questionnaire in patients receiving chemotherapy for solid tumors. BMC Cancer 2015;15:999.
[46] Hepatitis C guidance: AASLD-IDSA recommendations for testing, managing, and treating adults infected with hepatitis C virus. Hepatology 2015;62:932–54.
[47] Torres HA, Hosry J, Mahale P, Economides MP, Jiang Y, Lok AS. Hepatitis C virus reactivation in patients receiving cancer treatment: a prospective observational study. Hepatology 2018;67:36–47.
[48] Mahale P, Okhuysen PC, Torres HA. Does chemotherapy cause viral relapse in cancer patients with hepatitis C infection successfully treated with antivirals? Clin Gastroenterol Hepatol 2014;12:1051–4.
[49] Vannata B, Arcaini L, Zucca E. Hepatitis C virus-associated B-cell non-Hodgkin's lymphomas: what do we know? Ther Adv Hematol 2016;7:94–107.
[50] Pellicelli AM, Marignani M, Zoli V, Romano M, Morrone A, Nosotti L, et al. Hepatitis C virus-related B cell subtypes in non Hodgkin's lymphoma. World J Hepatol 2011;3:278–84.
[51] Merli M, Frigeri M, Gotti M, Grossi P, Bruno R, Passamonti F, et al. Direct-acting antivirals during or after immunochemotherapy in hepatitis C virus-positive diffuse large B-cell lymphomas. Hepatology 2017;66:1341–3.
[52] Kawamura Y, Ikeda K, Arase Y, Yatsuji H, Sezaki H, Hosaka T, et al. Viral elimination reduces incidence of malignant lymphoma in patients with hepatitis C. Am J Med 2007;120:1034–41.
[53] Marignani M, Marzano A, Begini P, Vitolo U, Luminari S, Levis A, et al. Perception of hepatitis B virus infection reactivation-related issues among specialists managing hematologic malignancies: result of an Italian survey. Leuk Lymphoma 2014;55:2564–71.
[54] Merli M, Visco C, Spina M, Luminari S, Ferretti VV, Gotti M, et al. Outcome prediction of diffuse large B-cell lymphomas associated with hepatitis C virus infection: a study on behalf of the Fondazione Italiana Linfomi. Haematologica 2014;99:489–96.

[55] Angelucci E, Muretto P, Nicolucci A, Baronciani D, Erer B, Gazlev J, et al. Effects of iron overload and hepatitis C virus positivity in determining progression of liver fibrosis in thalassemia following bone marrow transplantation. Blood 2002;100:17–21.
[56] Re A, Michieli M, Casari S, Allione B, Cattaneo C, Rupolo M, et al. High-dose therapy and autologous peripheral blood stem cell transplantation as salvage treatment for AIDS-related lymphoma: long-term results of the Italian Cooperative Group on AIDS and Tumors (GICAT) study with analysis of prognostic factors. Blood 2009;114:1306–13.
[57] Ennishi D, Maeda Y, Niitsu N, Kojima M, Izutsu K, Takizawa J, et al. Hepatic toxicity and prognosis in hepatitis C virus-infected patients with diffuse large B-cell lymphoma treated with rituximab-containing chemotherapy regimens: a Japanese multicenter analysis. Blood 2010;116:5119–25.
[58] Ennishi D, Terui Y, Yokoyama M, Mishima Y, Takahashi S, Takeuchi K, et al. Monitoring serum hepatitis C virus (HCV) RNA in patients with HCV-infected CD20-positive B-cell lymphoma undergoing rituximab combination chemotherapy. Am J Hematol 2008;83:59–62.
[59] Marignani M, Mangone M, Cox MC, Angeletti S, Veggia B, Ferrari A, et al. HCV-positive status and hepatitis flares in patients with B-cell non-Hodgkin's lymphoma treated with rituximab-containing regimens. Dig Liver Dis 2011;43:139–42.
[60] Evans AT, Loeb KR, Shulman HM, Hassan S, Qiu WC, Hockenbery DM, et al. Fibrosing cholestatic hepatitis C after hematopoietic cell transplantation: report of fatal cases. Am J Surg Pathol 2015;39:212–20.
[61] Visentini M, Fiorilli M, Casato M. From the pathogenesis to the cure of indolent B-cell lymphoproliferative disorders associated with hepatitis C virus infection: which role for direct-acting antivirals? Expert Rev Hematol 2017;10:719–72.
[62] Dreyling M, Thieblemont C, Gallamini A, Arcaini L, Campo E, Hermine O, et al. ESMO consensus conferences: guidelines on malignant lymphoma. Part 2: marginal zone lymphoma, mantle cell lymphoma, peripheral T-cell lymphoma. Ann Oncol 2013;24:857–77.
[63] Tarella C, Arcaini I, Baldini I, Barosi G, Billio A, Marchetti M, et al. Italian Society of Hematology, Italian Society of Experimental Hematology, and Italian Group for Bone Marrow Transplantation guidelines for the management of indolent, nonfollicular B-cell lymphoma (marginal zone, lymphoplasmacytic, and small lymphocytic lymphoma). Clin Lymphoma Myeloma Leuk 2015;15:75–85.
[64] Mallet V, van Bommel F, Doerig C, Pischke S, Hermine O, Locasciulli A, et al. Management of viral hepatitis in patients with haematological malignancy and in patients undergoing haemopoietic stem cell transplantation: recommendations of the 5th European Conference on Infections in Leukaemia (ECIL-5). Lancet Infect Dis 2016;16:606–17.
[65] NCCN guidelines, version 1, 2014: non-Hodgkin's lymphomas (2017 update). Available at: http://www.nccn.org/professionals/default.aspx.
[66] Merli M, Rattotti S, Gotti M, Arcaini L. Antiviral therapies for managing viral hepatitis in lymphoma patients. Expert Opin Pharmacother 2017;18:363–76.
[67] Torres HY, Chong PP, De Lima M, Friedman MS, Giralt S, Hammond SP, et al. Hepatitis C virus infection among hematopoietic cell transplant donors and recipients: American Society for Blood and Marrow Transplantation task force recommendations. Biol Blood Marrow Transplant 2015;21:1870–82.
[68] ESMO handbook on cancer treatment in special clinical situations. ESMO Publishing Working Group; 2013.
[69] Terrault NA, McCaughan GW, Curry MP, Gane E, Fagiuli S, Fung JYY, et al. International liver transplantation society consensus statement on hepatitis C management in liver transplant candidates. Transplantation 2017;101:945–55.
[70] Burra P, Belli LS, Ginanni Corradini S, Volpes R, Marzioni M, Giannini E, et al. Common issues in the management of patients in the waiting list and after liver transplantation. Dig Liver Dis 2017;49:241–53.
[71] Gane E. The natural history and outcome of liver transplantation in hepatitis C virus-infected recipients. Liver Transpl 2003;9:S28–34.
[72] Berenguer M, Schuppan D. Progression of liver fibrosis in post-transplant hepatitis C: mechanisms, assessment and treatment. J Hepatol 2013;58:1028–41.
[73] Forman LM, Lewis JD, Berlin JA, Feldman HI, Lucey MR. The association between hepatitis C infection and survival after orthotopic liver transplantation. Gastroenterology 2002;122:889–96.
[74] Terrault NA, Berenguer M, Strasser SI, Gadano A, Lilly L, Samuel D, et al. International liver transplantation society consensus statement on hepatitis C management in liver transplant recipients. Transplantation 2017;101:956–67.
[75] Pascasio JM, Vinaixa C, Ferrer MT, Colmenero J, Rubin A, Castells L, et al. Clinical outcomes of patients undergoing antiviral therapy while awaiting liver transplantation. J Hepatol 2017;67:1168–76.
[76] Afdhal N, Everson GT, Calleja JL, McCaughan GW, Bosch J, Brainard DM, et al. Effect of viral suppression on hepatic venous pressure gradient in hepatitis C with cirrhosis and portal hypertension. J Viral Hepat 2017;24:823–31.
[77] Lens S, Alvarado E, Marino Z, Londono MC, LLop E, Martinez J, et al. Effects of all-oral anti-viral therapy on HVPG and systemic hemodynamics in patients with hepatitis C virus-associated cirrhosis. Gastroenterology 2017;153:1273–83.
[78] Belli LS, Berenguer M, Cortesi PA, Strazzabosco M, Rockenschaub SR, Martini S, et al. Delisting of liver transplant candidates with chronic hepatitis C after viral eradication: a European study. J Hepatol 2016;65:524–31.
[79] Charlton M, Everson GT, Flamm SL, Kumar P, Landis C, Brown RS, et al. Ledipasvir and sofosbuvir plus ribavirin for treatment of HCV infection in patients with advanced liver disease. Gastroenterology 2015;149:649–59.
[80] Foster GR, Irving WL, Cheung MC, Walker AJ, Hudson BE, Verma S, et al. Impact of direct acting antiviral therapy in patients with chronic hepatitis C and decompensated cirrhosis. J Hepatol 2016;64:1224–31.
[81] Guarino M, Morisco F, Valvano MR, Ippolito Am, Librandi M, Andriulli N, et al. Systematic review: interferon-free regimens for patients with HCV-related child C cirrhosis. Aliment Pharmacol Ther 2017;45:1193–200.
[82] Tapper EB, Afdhal NH, Curry MP. Before or after transplantation? A review of the cost effectiveness of treating waitlisted patients with Hepatitis C. Transplantation 2017;101:933–7.
[83] European Association for the Study of the Liver. EASL guidelines on hepatitis C. J Hepatol 2018;69:461–511.
[84] Pawlotsky JM. Hepatitis C virus resistance to direct-acting antiviral drugs in interferon-free regimens. Gastroenterology 2016;151:70–86.
[85] Belli LS, Duvoux C, Berenguer M, Berg T, Coilly A, Colle I, et al. ELITA consensus statements on the use of DAAs in liver transplant candidates and recipients. J Hepatol 2017;67:585–602.
[86] Cholankeril G, Li AA, Yoo ER, Ahmed A. Direct-acting antiviral therapy and improvement in graft survival of hepatitis C liver transplant recipients. Transplantation 2017;101:e349.
[87] Beckebaum S, Cicinnati VR, Radtke A, Kabar I. Calcineurin inhibitors in liver transplantation — still champions or threatened by serious competitors? Liver Int 2013;33:656–65.
[88] Toniutto P, Zanetto A, Ferrarese A, Burra P. Current challenges and future directions for liver transplantation. Liver Int 2017;37:317–27.
[89] Coilly A, Samuel D. Pros and cons: usage of organs from donors infected with hepatitis C virus — revision in the direct-acting antiviral era. J Hepatol 2016;64:226–31.
[90] Gasink LB, Blumberg EA, Localio AR, Desai SS, Israni AK, Lautenbach E. Hepatitis C virus seropositivity in organ donors and survival in heart transplant recipients. J Am Med Assoc 2006;296:1843–50.
[91] Cotler SJ, Jensen DM, Kesten S. Hepatitis C virus infection and lung transplantation: a survey of practices. J Hear Lung Transplant 1999;18:456–9.
[92] Lunel F, Cadranel JF, Rosenheim M, Dorent R, Di-Martino V, Payan C, et al. Hepatitis virus infections in heart transplant recipients: epidemiology, natural history, characteristics, and impact on survival. Gastroenterology 2000;119:1064–74.
[93] Fagiuoli S, Minniti F, Pevere S, Farinati F, Burra P, Livi U, et al. HBV and HCV infections in heart transplant recipients. J Hear Lung Transpl 2001;20:718–24.
[94] Fagiuoli S, Cooper DKC, Zuhdi N. Hepatitis C status of heart transplant recipients. Clin Transpl 1998;12:5–10.
[95] Preiksaitis JK, Cockfield SM, Fenton JM, Burton NI, Chui LW. Serologic responses to hepatitis C virus in solid organ transplant recipients. Transplantation 1997;64:1775–80.
[96] Wells JT, Lucey MR, Said A. Hepatitis C in transplant recipients of solid organs, other than liver. Clin Liver Dis 2006;10:901–17.
[97] Miguel M, Sampaio M, Kuo HT, Poommipanit N, Martin P, Bunnapradist S. Influence of preexisting hepatitis C virus antibody positivity in simultaneous pancreas-kidney transplant recipients. Transplantation 2010;90:61–7.
[98] Fagiuoli S, Pevere S, Minniti F, Livi U, Caforio AL, Naccarato R, et al. Natural leukocyte interferon alfa for the treatment of chronic viral hepatitis in heart transplant recipients. Transplantation 2003;75:982–6.
[99] Lin MH, Chou NK, Chi NH, Chen YS, Yu HY, Huang SC, et al. The outcome of heart transplantation in hepatitis C-positive recipients. Transpl Proc 2012;44:890–3.
[100] Shafii AE, Su JW, Smedira NG, Navia JL, Taylor DO, Starling RC, et al. The effect of recipient hepatitis C virus infection on outcomes following heart transplantation. Transplant Proc 2010;42:1784–7.
[101] Kumar S, Deo SV, Altarabsheh SE, Dunlay SM, Sarabu N, Sareyyupoglu B, et al. Effect of hepatitis C positivity on survival in adult patients undergoing heart transplantation (from the United Network for Organ Sharing Database). Am J Cardiol 2016;118:132–7.
[102] Lee I, Localio R, Brensinger CM, Blumberg EA, Lautenbach E, Gasink L, et al. Decreased post-transplant survival among heart transplant recipients with pre-transplant hepatitis C virus positivity. J Hear Lung Transplant 2011;30:1266–74.
[103] Fong TL, Cho YW, Hou L, Hutchinson IV, Barbers RG, Herrington CS. Outcomes after lung transplantation and practices of lung transplant programs in the United States regarding hepatitis C seropositive recipients. Transplantation 2011;91:1293–6.
[104] Doucette KE, Halloran K, Kapasi A, Lien D, Weinkauf JG. Survival following lung transplantation in not impacted by hepatitis C infection. Am J Transpl 2016;16:2445–52.
[105] Sahi H, Zein NN, Mehta AC, Blazey HC, Meyer KH, Budev M. Outcomes after lung transplantation in patients with chronic hepatitis C virus infection. J Heart Lung Transplant 2007;26:466–71.
[106] Koenig A, Stepanova M, Saab S, Ahmed A, Wong R, Younossi ZM. Long-term outcomes of lung transplant recipients with hepatitis C infection: a retrospective study of the U.S. transplant registry. Aliment Pharmacol Ther 2016;44:271–8.
[107] Honaker MR, Stratta RJ, Lo A, Egidi MF, Shokouh-Amiri MH, Grewal HP, et al. Impact of hepatitis C virus status in pancreas transplantation: a case controlled study. Clin Transpl 2002;16:243–51.
[108] Gonzalez S, Trotter JF. The rise of the opioid epidemic and hepatitis C positive organs: a new era in liver transplantation. Hepatology 2018;67:1600–8.

[109] Goldberg DS, Abt PL, Blumberg EA, Van Deerlin VM, Levine M, Reddy KR, et al. Trial of transplantation of HCV-infected kidneys into uninfected recipients. N Engl J Med 2017;376:2394–5.
[110] Gottlieb RL, Sam T, Wada SY, Trotter JF, Asrani SK, Lima B, et al. Rational heart transplant from hepatitis C donor: new antiviral weapons conquer the trojan. J Card Fail 2017;23:765–7.
[111] Isnard Bagnis C, Couchoud C, Bowens M, Sarraj A, Deray G, Tourret J, et al. Epidemiology update for hepatitis C virus and hepatitis B virus in end-stage renal disease in France. Liver Int 2017;37:820–6.
[112] Kliem V, Burg M, Haller H, Suwelack B, Adendroth D, Fritsche L, et al. Relationship of hepatitis B or C virus prevalences, risk factors, and outcomes in renal transplant recipients: analysis of German data. Transplant Proc 2008;40:909–14.
[113] Terrault NA, Adey DB. The kidney transplant recipient with hepatitis C infection: pre- and posttransplantation treatment. Clin J Am Soc Nephrol 2007;2:563–75.
[114] Fabrizi F, Lunghi G, Ganeshan SV, Martin P, Messa P. Hepatitis C virus infection and the dialysis patient. Semin Dial 2007;20:416–22.
[115] Molnar MZ, Alhourani HM, Wall BM, Lu JL, Streja E, Kalantar-Zadeh K, et al. Association of hepatitis C viral infection with incidence and progression of chronic kidney disease in a large cohort of US veterans. Hepatology 2015;61:1495–502.
[116] Soriano V, Labarga P, Fernandez-Montero JV, de Mendoza C, Esposito I, Benitez-Gutierrez L, et al. Hepatitis C cure with antiviral therapy-benefits beyond the liver. Antivir Ther 2016;21:1–8.
[117] Colombo M, aghemo A, Liu H, Zhang J, Dvory-Sobol H, Hyland R, et al. Treatment with ledipasvir-sofosbuvir for 12 or 24 weeks in kidney transplant recipients with chronic hepatitis C virus genotype 1 or 4 infection: a randomized trial. Ann Intern Med 2017;166:109–17.
[118] Roth D, Ladino M. Transplantation of kidneys from HCV-positive donors: how to best use a scarce resource. J Am Soc Nephrol 2017;28:3139–41.
[119] Rivera J, Garcia-Monforte A, Pineda A, Millan Nunez-Cortes J. Arthritis in patients with chronic hepatitis C virus infection. J Rheumatol 1999;26:420–4.
[120] Taglione E, Vatteroni MI, Martini P, Galluzzo E, Lombardini F, Delle Sedie A, et al. Hepatitis C virus infection: prevalence in psoriasis and psoriatic arthritis. J Rheumatol 1999;26:370–2.
[121] Coppola N, Pisaturo M, Guastafierro S, Tonziello G, Sica A, Iodice V, et al. Increased hepatitis C viral load and reactivation of liver disease in HCV RNA-positive patients with onco-haematological disease undergoing chemotherapy. Dig Liver Dis 2012;44:49–54.
[122] Cacoub P, Commarmond C, Sadoun D, Desbols AC. Hepatitis C virus infection and rheumatic diseases: the impact of direct-acting antiviral agents. Rheum Dis Clin North Am 2017;43:123–32.
[123] Di Domenicantonio R, Cappai G, Arcà M, Agabiti N, Kohn A, Vernia P, et al. Occurrence of inflammatory bowel disease in central Italy: a study based on health information systems. Dig Liver Dis 2014;46:777–82.
[124] Allen AM, Kim WR, Larson J, Loftus Jr EV. Efficacy and safety of treatment of hepatitis C in patients with inflammatory bowel disease. Clin Gastroenterol Hepatol 2013;11:1655–60.
[125] Brunasso AM, Puntoni M, Gulia A, Massone C. Safety of anti-tumour necrosis factor agents in patients with chronic hepatitis C infection: a systematic review. Rheumatology (Oxford) 2011;50:1700–11.
[126] Mazzola G, Macaluso FS, Adamoli I, Renna S, Cascio A, Orlando A. Diagnostic and vaccine strategies to prevent infections in patients with inflammatory bowel disease. J Infect 2017;74:433–41.
[127] Cadranel JF, Grippon P, Lunel F, Desruennes M, Leger P, Azar N, et al. Chronic liver dysfunction in heart transplant recipients, with special reference to viral B, C, and non-A, non-B, non-C hepatitis. A retrospective study in 80 patients with follow-up of 60 months. Transplantation 1991;52:645–50.