Hepatol Int
DOI 10.1007/s12072-012-9342-y

GUIDELINES

APASL consensus statements and management algorithms for hepatitis C virus infection

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Received: 14 September 2011 / Accepted: 21 January 2012

Abstract The Asian Pacific Association for the Study of the Liver (APASL) convened an international working party on the "APASL Consensus Statements and Management Algorithms for Hepatitis C Virus Infection" in December, 2010, in order to revise "Asian Pacific Association for the Study of the Liver consensus statements on the diagnosis, management and treatment of hepatitis C virus infection (J Gastroenterol Hepatol 22:615–633, 2007)". The working party consisted of expert hepatologists from the Asian-Pacific region gathered at Makuhari, Chiba, Japan on 19 December 2010. New data were presented, discussed and debated to draft a revision. Participants of the consensus meeting assessed the quality of cited studies. Finalized recommendations are presented in this review.

Keywords APASL · DAAs · Guideline · HCV · Treatment

Laboratory testing for HCV infection and fibrosis

Serologic assays

Exposure to hepatitis C virus (HCV) is usually determined by testing for specific antibodies (anti-HCV antibodies) by using an approved enzyme or chemiluminescent immunoassay

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Published online: 01 March 2012

(EIA or CIA). However, antibodies might not be detectable in the first few weeks after initial infection (window period), in patients who are immunosuppressed or in patients in whom resolution of HCV infection occurs over many years [1–7].

Recently, commercial HCV core antigen assays, which show a good correlation with HCV RNA assays, have become available. In some circumstances, these might be an alternative to HCV RNA assays, but due to limited sensitivity, the major role of these assays might be in the identification of blood donors in the seroconversion window. The detection limits of the HCV core antigen assay kit of Ortho Diagnostics and Abbott Diagnostics are 44 and 3 fmol/L, respectively. These assays are currently expensive and available in limited countries, but might be available in Asian countries in the near future [8–11].

Molecular assays

HCV genotyping

HCV genotyping is helpful in epidemiologic studies and necessary for clinical application of personalized therapy for chronic hepatitis C (CHC) [7]. Currently, HCV has been classified into six major genotypes, which can be further divided into subtypes. Genotypes 1, 2, and 3 are widely distributed in the Asia-Pacific region, whereas genotypes 4 and 6 are mainly restricted to the Middle-East and Southeast regions, respectively [12, 13].

Pegylated interferon (peginterferon) plus ribavirin combination therapy has been the standard of care (SOC) for treatment of CHC, and improved outcomes have been achieved using genotype- and response-guided therapy by determination of virus genotype and on-treatment virological responses.

A new generation line probe assay designed with both 5′ UTR and core-specific oligonucleotides has been shown to overcome the inability to distinguish HCV genotype 6c-l [14, 15].

Qualitative HCV RNA testing

HCV RNA is used in determining acute or chronic infection, assessing anti-HCV indeterminate samples, and monitoring and assessing responses to antiviral therapy. HCV RNA testing should be strongly considered in patients at high risk of infection, but who might be anti-HCV negative or indeterminate because they are in the early phase of acute HCV infection or are immunosuppressed (such as patients on hemodialysis or with HIV infection).

The assays used for qualitative HCV RNA testing included end-point PCR and transcription-mediated amplification (TMA) with detection limits of 50 and 10 IU/mL, respectively. Although negative TMA results were more predictive of sustained virological response (SVR), a single positive TMA result should be interpreted with caution, because patients with positive TMA results may achieve SVR [16].

Recently, with the introduction of more sensitive quantitative real-time PCR assays, qualitative assays may be no longer needed.

Quantitative HCV RNA testing

HCV viral loads do not appear to be associated with disease activity and progression to chronicity. One study has indicated an association between HCV viral loads and development of hepatocellular carcinoma (HCC) in a prospective community-based cohort [17].

Notably, viral load has been shown to be a prognostic indicator of therapy outcome. Monitoring viral load during therapy has also proven useful in individualized HCV therapy. Response-guided therapy based on on-treatment virological responses could provide information about optimal treatment durations and help maximize cost-effectiveness and minimize adverse events [18–22]. A recent study has shown that HCV RNA levels after 4 weeks of peginterferon plus ribavirin therapy (lead-in period) could predict not only treatment outcome, but also the development of drug resistance with subsequent addition of a protease inhibitor to the treatment regimen [23].

Recently introduced real-time PCR assays with a broad dynamic range of quantification are sensitive, specific, precise, and reproducible. Cobas Ampliprep/Cobas TaqMan is the first FDA-approved real-time PCR assay. However, wide application of this assay requires careful monitoring of HCV-4-infected patients because the assay might underestimate HCV RNA levels in HCV-4-positive samples [24, 25].

Highly sensitive assays have been reported, such as the VERSANT HCV RNA Qualitative Assay (HCV Qual [TMA], Siemens Healthcare Diagnostics, Saint Denis, France) with a detection limit of 9.6 IU/mL and TaqMan 2.0 assay (Roche Diagnostics) with limits of quantification and detection of 25 and 9.3 IU/mL, respectively [26, 27]. Another real-time PCR assay, Abbott Real-Time HCV assay (RealTime HCV; Abbott Molecular, Des Plaines, IL, USA) with limits of quantification of 12 IU/mL, has been approved by FDA for on-treatment monitoring of HCV RNA levels as an aid in the management of HCV therapy [28]. These assays will be useful in clinical practice in Asian countries.

Dried blood spots

Poor uptake of HCV test materials in injecting drug users (injection drug users; intravenous drug users: IDUs) is

problematic. Dried blood spots (DBSs), which are sampled using a disposable lancet and stable at room temperature, could be employed as first-line diagnostic specimens and are suitable for diagnostic as well as surveillance purposes, especially when freezing equipment is not available. DBS sampling could enhance the public health surveillance of HCV among IDUs and might allow differentiation between individuals with cleared infection, ongoing infection, and recent infection. However, DBS nucleic acid amplification technology (NAT) is not recommended for monitoring treatment responses, because of a tenfold reduction in viral loads yield [29, 30].

Assessment of liver fibrosis

Assessment of liver fibrosis is important clinically for decision making. Although liver biopsy remains the "gold standard" to assess liver fibrosis, alternative noninvasive approaches to liver fibrosis have assumed great importance. These include [31, 32]:

- Noninvasive imaging (e.g., transient elastography).
- Noninvasive blood marker panels (e.g., aspartate aminotransferase–platelet ratio index (APRI), FibroTest, FIBROSpect II, Hepascore, FibroMeter, and FibroFast).

Although noninvasive markers and transient elastography are useful for identifying only those patients with no fibrosis or with advanced fibrosis, a stepwise algorithm incorporating noninvasive markers and/or transient elastography may enhance the accuracy of diagnosis and reduce a significant number of liver biopsies [33–35]. Furthermore, accumulating data provide evidence that noninvasive methods of assessing liver fibrosis can be applied at a single point or repeatedly to provide prognostically meaningful distinctions in predicting clinical outcomes, with and without antiviral therapy, in CHC patients [36–41]. Algorithm incorporating noninvasive methods for clinical practice remains to be established.

Consensus statements: HCV infection and laboratory testing

1. Anti-HCV antibody testing should be conducted with approved anti-HCV third- or fourth-generation EIA or CIA (II-2)*.
2. Samples that test negative with an approved EIA/CIA can be reported as anti-HCV negative. However, it should be noted that individuals on hemodialysis or those coinfected with HIV might be HCV RNA positive, but anti-HCV negative (II-2).
3. Samples reactive in an approved single EIA can be reported as anti-HCV positive, provided the signal-to-cutoff ratio is sufficiently high to be predictive of a true positive (III).
4. For samples that do not reach this threshold or have reactivity close to the cutoff, a sensitive HCV RNA test should be considered and/or a further follow-up sample be obtained for both anti-HCV and HCV RNA NAT (III).
5. HCV RNA testing requires appropriate contamination controls (II-2).
6. A dedicated sample/aliquot not derived from other test samples is preferred for HCV RNA testing (II-2).
7. HCV RNA quantitation should be reported in IU/mL (optional to include copies/mL) (III).
8. Monitoring of HCV loads during treatment is important for response-guided therapy to determine treatment protocol and duration (I).
9. HCV genotype testing is important for assessing treatment duration and efficacy of antiviral therapy. The use of primers targeting both the 5′ UTR and core region is recommended to distinguish some of the genotype 6 subtypes, prevalent in Southeast Asia, from genotype 1 or 1b (II-2).
10. Participation in an external quality assurance program for all testing is ideal (II-2).
11. Internal quality assurance testing is required for all testing (II-2).
12. Testing DBSs that are sampled with a disposable lancet and are stable at room temperature could enhance the public health surveillance of HCV among IDUs (II-2).
13. Noninvasive methods for liver fibrosis are useful for identifying patients with no fibrosis or advanced fibrosis and can provide prognostically meaningful distinctions in predicting clinical outcomes in CHC patients. A stepwise algorithm incorporating noninvasive methods may enhance the accuracy of diagnosis and reduce a significant number of liver biopsies (II-2).

*Numbers in parentheses refer to levels of evidence [5]. *EIA* enzyme immunoassay, *CIA* chemiluminescent immunoassay, *DBS* dried blood spot.

The original guidelines were published in [7]. Points 1, 2, 4, 5, 6, 8, 9, 12, and 13 are revised or new recommendations.

Prevention of HCV infection

The World Health Organization estimates that as many as 170 million persons worldwide might be infected with HCV [42], with prevalence in Southeast Asia at 2.2% and in the Western Pacific at 3.9% [42]. However, these are

crude estimates with significant differences in prevalence rates within provinces even in the same country.

True prevention of HCV can only be achieved with an effective prophylactic vaccine, but vaccine trials are in the early phase or in progress [43]. Consequently, the current objective of HCV prevention is to reduce transmission through identification and reduction of risk factors. Transmission risk stems from inoculation through the skin or mucous membranes; thus, certain types of risk groups should be identified, such as people with skin or mucous membrane inoculation, or with exposure of broken skin to contaminated blood (household contact, dental work) [44].

In the developing world [45, 46], blood transfusion and intravenous drug use are important, but additional transmission groups include acupuncture, body piercing, unsafe injection practices, and familial transmission.

Blood safety

In 1992, the introduction of second-generation anti-HCV ELISA largely eliminated HCV transmission by screening out infected donors. Nucleic acid testing has reduced the risk of HCV transmission to 0.1–2.33 per million donations [47, 48]. However, the Global Database on Blood Safety shows that testing with anti-HCV ELISA is insufficient, particularly in countries with low human development index—only 51.3% of units of blood are tested for HCV [49].

IDUs

Globally, there is variation in the estimated HCV prevalence rates among IDUs—10–100% in South and Southeast Asia, and 34–93% in East Asia and the Pacific region [50].

In a systematic review, Hagan et al. [51] found no clear association of HCV prevalence with duration of injection use or with age of users. Further, an increased risk of HCV infection was found in non-injecting drug users with the following risk factors: sharing of inhalation tubes for crack cocaine (adjusted odds ratio 3.6, 95%CI 1.3–9.8), presence of tattoos (adjusted odds ratio 3.5, 95%CI 1.3–9.1), and age >34 years (adjusted odds ratio 3.9, 95%CI 1.3–11.6) [52]. Since HCV can be transmitted via needles and syringes as well as drug preparation equipment, a key question was whether the provision of sterile injecting equipment was effective in reducing transmission. A review of meta-analyses concluded that there was insufficient evidence that such interventions were effective [53]. Although the relative risk of HCV infection associated with drug preparation equipment was between 2.0 and 5.9, there exists the limitation of the "sterility" from needle and syringe exchange programs [54].

Hemodialysis

Hemodialysis units are notorious for HCV outbreaks that are almost certainly attributable to safety breaches [55]. The Centers for Disease Control (CDC) have issued recommendations for infection control in such units [56], but a survey of practices revealed that compliance with these recommendations was suboptimal [57]. Absence of de novo HCV infections in hemodialysis units can, however, be achieved by strict adherence to universal hygiene precautions [58].

Medical procedures

According to the Hep-Net acute HCV database, 15% of acute HCV infections are due to medical procedures, while another 13% are caused by needlestick injuries [58]. Such outbreaks are inevitably due to breach of standard safety precautions [49] and involve multi-vial sampling, capillary blood sampling, surgical procedures [59], gastrointestinal endoscopy [60], radiopharmaceuticals [61], and oncology procedures.

Unsafe injection practices

This is a poorly documented field, but very important in the developing world. A list of unsafe injection practices has been summarized by Kermode [62]. In a meta-analysis, unsafe injection practices were found to be widespread in the developing world and accounted for >50% of injections. Moreover, in Asia, 82% of injections administered were considered unnecessary [63, 64].

Other practices

A meta-analysis showed that body piercing was associated with an odds ratio of 1.7–2.7 of acquiring HCV [65]. Another meta-analysis of 124 studies showed that tattooing [66] carried an odds ratio of 2.8 (95%CI 2.4–3.2) of acquiring HCV. Finally, a meta-analysis of acupuncture studies [67] showed a modest risk of HCV infection with odds ratio of 1.3–3.3 with a possible relationship to having more than ten sessions.

Familial, sexual, and perinatal transmission

A meta-analysis [68] showed that the odds ratio of HCV transmission to the siblings and household contacts of HCV-infected chronic liver disease patients was 9.8 (95%CI 0.9–ad infinitum), while that to the offspring of Japanese HCV carriers was 1.8 (95%CI 1.2–2.6). Male

partners seemed to be more susceptible than female partners of HCV-infected males (odds ratio, 20.5; 95%CI 6.1–84.1). The vertical transmission rate was 6.2% in a cohort study of 1,787 mother–child pairs, and cesarean section was not protective [69]. This was confirmed in a meta-analysis [70]. The sexual transmission risk is controversial, and a meta-analysis [71] showed no risk in stable heterosexual relationships, but increased risk in those with multiple sexual partners and in HIV-positive gay men. A large sero-epidemiological study of 1,527 female commercial sexual workers from Korea reported an HCV prevalence of only 1.4% with no increased risk due to sexual activity [72], while in a study of 1,699 non-IDU gay men, only 1.5% tested anti-HCV positive, suggesting no increased risk in non-IDU gay men [73].

Consensus statements: prevention of HCV infection

1. All countries must introduce universal screening of blood donors for anti-HCV antibodies, with third- or fourth-generation EIA or CIA*. Regular audit procedures should be implemented to ensure compliance at blood-testing facilities. More data on the cost-effectiveness of nucleic acid testing for universal screening of blood products is required (II-2).
2. In health-care settings, adherence to universal precautions for infection control is essential. Regular audit procedures should be implemented to ensure compliance. These should include use of disposable or adequately sterilized materials for invasive procedures, and adequate cleansing and sterilization of instruments (II-2).
3. As transmission of HCV via IDUs is an increasing trend in the Asia-Pacific region, effective strategies to reduce HCV transmission in this group should be explored. Persons undergoing skin/mucosal penetrating procedures such as body piercing, tattooing, and acupuncture should be advised on the increased risk of HCV transmission (II-2).
4. The risk of sexual transmission is unclear, but the use of barrier contraception to reduce potential transmission may be prudent in those who have multiple sexual partners (III).
5. Unnecessary and unsafe injection practices are widely used in the developing world. It is important to reduce unnecessary injections (II-2) and carry out injections using recommended safe procedures.

**EIA* enzyme immunoassay; *CIA* chemiluminescent immunoassay; *IDU* injection drug user, injecting drug users, or intravenous drug user. The original guidelines were published in [7]. All the above points are revised or new recommendations.

Natural history of HCV infection

Acute HCV infection

In the USA, approximately 17% of all new cases of HCV per year present as symptomatic acute hepatitis, based on estimates from the CDC Sentinel Counties Study [74]. However, the overall incidence of HCV infection, and therefore of acute hepatitis C, is decreasing in the Western world in general. The true incidence of acute hepatitis C in the Asia-Pacific region is not well known and needs to be studied, although it is understood that in many countries in the region, HCV infection is on the rise and yet to reach its peak, let alone decline [75].

The average incubation period is around 7 weeks [76], and the clinical illness in most cases has a benign initial course. Fulminant hepatic failure is very uncommon and occurs in <1% of patients [77–83]. Patients usually present with jaundice, a flu-like illness, nausea or vomiting, and pain in the right upper abdominal quadrant [84]. In some studies, however, including one from Japan [85], jaundice has been reported only in a small number of patients, and maximal levels of serum bilirubin are in the range of 3–8 mg/dL. There is a modest rise in serum liver enzyme levels, as compared to other causes of acute hepatitis, e.g., hepatitis A or E virus infection.

The diagnosis of acute HCV infection remains problematic, as there is no definitive test. Antibodies of the IgM type do develop against the HCV core antigen, but they could also persist in chronic infection. In one study [86], however, serial determinations of IgM antibodies to HCV core antigen could be used to determine the presence of acute HCV infection. A definitive diagnosis of acute HCV infection can only be made if a patient who had been confirmed to be HCV antibody/HCV PCR negative prior to clinical illness becomes HCV PCR positive during clinical illness and then develops anti-HCV antibodies within 12 weeks. HCV RNA can be detected in serum within 1–2 weeks after exposure, increase progressively, and peak before the development of symptoms. Acute infection is also associated with fluctuation of HCV RNA levels and low HCV RNA levels [87].

A significant number of patients with acute HCV infection (up to 50%) can be expected to clear the virus spontaneously within the first 12 weeks of the onset of clinical illness [88]. Previously suggested determinants of spontaneous clearance have been symptomatic patients with jaundice who are also Caucasian [89], female patients [90], those infected with HCV genotype 3 [91], and those with low HCV levels [92]. More recently, a powerful genetic marker, the IL28B polymorphisms, has been associated with HCV clearance following acute infection. A number of studies based either on retrospective patient

cohorts with spontaneous clearance or those with acute HCV infection have documented the beneficial role of the CC allele of the single nucleotide polymorphism (SNP) rs12979860 at the IL28B locus in the clearance of HCV infection [93–95], and this effect seems independent of other biologic parameters associated with higher rates of HCV clearance. It has been reported that 50–80% of patients with acute hepatitis C will develop chronic infection [96]. Favorable IL28B genotypes are overpresented among HCV-non-1 versus HCV-1 infected patients, both Caucasian [94] and Asian [97], and probably contribute to the higher proportion of HCV-non-1 distribution in Asian areas [98].

Chronic HCV infection

In chronic HCV infection, the progression of hepatic fibrosis is slow, but steady in many cases [99–109]. Several studies indicate that the fibrosis progression rate is 0.10–0.13 U/year in untreated patients [110–113].

Cirrhosis rates become significant after 20 years of infection. Some studies estimate that up to 20–30% of patients will develop a progressive liver disease leading to cirrhosis and hepatocellular carcinoma (HCC) [96]. HCC rates become significant after 30 years of infection [7]. Factors associated with disease progression [7] include duration of infection, age [114] at the time of acquiring infection, sex, alcohol consumption [96, 115], immunosuppression (e.g., HIV coinfection or organ transplant recipients) [116, 117], obesity [118], insulin resistance [119, 120], coinfection with other viruses [121], elevated aminotransferases [122], and genetic factors [123]. Although elevated ALT levels suggest active liver damage, normal ALT levels do not exclude significant liver disease [7]. Progression to cirrhosis can be best predicted on baseline histological parameters such as the activity of necroinflammation and stage of fibrosis [7, 124]. Once patients develop cirrhosis, HCC develops at approximately 1–7% per year and is increased in patients with raised alpha-fetoprotein levels at baseline [96, 124].

Consensus statements: natural history of HCV infection

1. Acute hepatitis C is a well-recognized entity. In the stage of acute hepatitis, patients should be monitored for spontaneous viral clearance. Patients with symptomatic acute hepatitis and female patients are more likely to clear the virus. A definitive diagnosis of acute HCV infection can be made in a patient known to be HCV antibody/RNA negative, who develops a symptomatic illness and becomes HCV PCR positive and subsequently HCV antibody positive. Up to 50% of patients with acute HCV infection may clear the virus spontaneously, most often within the first 12 weeks of symptomatic illness. A CC genotype of the SNP rs12979860 at the IL28B locus has emerged as a powerful determinant of spontaneous HCV clearance. Spontaneous clearance is also more likely in symptomatic patients, women, and those infected with HCV genotype 3.
2. In chronic HCV infection, elevated serum ALT level suggests progressive liver damage. However, normal ALT level does not exclude significant liver disease. The liver fibrosis progression rate is 0.10–0.13 U/year in untreated patients.
3. In chronic HCV infection, it is well recognized that excessive alcohol and insulin resistance are associated with disease progression. It is recommended that patients consume less than the WHO guidelines for alcohol intake, and that obesity and insulin resistance be controlled through exercise and dietary intervention to achieve ideal BMI (II-2).
4. In patients with HCV-related liver cirrhosis, the risk of hepatic decompensation is approximately 3–4% per year and 1.4–6.9% per year for HCC. In chronic HCV infection, a surveillance program for the early detection of HCC should be offered. Invasive or noninvasive procedures may predict progression toward liver fibrosis and cirrhosis. Staging of fibrosis with transient elastography with or without liver biopsy may enable early prediction of HCC occurrence (II-2).

The original guidelines were published in [7]. Points 1, 2, and 4 are revised or new recommendations.

Treatment of HCV infection

Before a discussion of specific therapies, some general points need to be made [7]. Alcohol intake should be discouraged during treatment. Hepatitis A and B immunization should be advised in patients not immune to hepatitis A virus and hepatitis B virus (HBV) [7]. A liver biopsy is useful in some patients. Noninvasive procedures such as transient elastography and liver fibrosis markers, which are commercially available, may also provide important information about liver fibrosis and guide treatment. Table 1 shows contraindications for anti-HCV therapy.

The definition of responses to antiviral treatment is shown in Table 2. Sustained virological response (SVR) is the best correlate of beneficial changes, and it has been shown to have the following beneficial effects [7]: (1) fibrotic regression [125, 126]; (2) substantially reduced rate of HCC [127–129]; (3) decreased rate of other complications, including liver failure, liver-related death [130, 131], and liver-unrelated death [132]; and (4) improved quality

Table 1 Contraindications for the use of peginterferon alfa and ribavirin [7]

Absolute contraindications
Present or past psychosis or severe depression
Uncontrolled seizures
Hepatic decompensation
Pregnancy (ribavirin)
Renal failure (ribavirin)
Severe heart disease (ribavirin)
Relative contraindications
History of depression
Uncontrolled diabetes mellitus
Uncontrolled hypertension
Retinopathy
Psoriasis
Autoimmune thyroiditis or other active autoimmune disorders including autoimmune hepatitis
Symptomatic heart disease or severe vascular disease (ribavirin)
Anemia/ischemic vascular disease (ribavirin)
Conditions requiring special caution for interferon administration
Neutropenia (neutrophil count <1,500 cells/μL)
Thrombocytopenia (platelet count <85,000/μL)
Organ transplantation
History of autoimmune disease
Presence of thyroid autoantibodies
Age >70 years

of life [132]. Specific issues regarding therapy in acute and chronic HCV infection will now be addressed.

Acute hepatitis C

In acute HCV infection, serum HCV RNA is usually detected before the appearance of anti-HCV antibodies and is often the only diagnostic indicator of this condition [7]. Acute HCV infection often becomes chronic, especially in asymptomatic individuals. However, the infection spontaneously resolves in up to 50% of patients who present with symptoms [7]. Female sex, favorable SNP of IL28B, and infection with HCV genotype non-1 increase the chance of spontaneous resolution.

Spontaneous resolution is less likely after 12 weeks of infection [7]. Treatment of hepatitis C in the acute stage has resulted in better SVR rates than treatment in the chronic stage. The objective of antiviral treatment in acute hepatitis C is to prevent the development of CHC [7].

Studies using conventional interferons [133, 134] as well as those using peginterferon alfa [135–137] for 24 weeks, have achieved high rates of SVR in acute hepatitis C. Addition of ribavirin to interferon alfa or peginterferon alfa has not resulted in significant improvement in SVR rates [7]. HCV genotypes 2, 3, and 4 respond better than HCV genotype 1, and peginterferon alfa administration can reduce treatment time to 12 weeks in patients

Table 2 Definitions of responses to treatment and the level of HCV RNA

Abbreviations	Terms	Descriptions
LVL	Low viral load	HCV RNA < 400,000 IU/mL
HVL	High viral load	HCV RNA > 400,000 IU/mL
RVR	Rapid virological response	Non-detectability of HCV RNA (<50 IU/mL) after 4 weeks of therapy
eRVR	Extended rapid virological response	Non-detectability of HCV RNA at week 4 and at week 12
EVR	Early virological response	cEVR or pEVR (see below)
cEVR	Complete EVR	Non-detectability of HCV RNA (<50 IU/mL) after 12 weeks of therapy
pEVR	Partial EVR	At least a 2 $\log_{10}$ decrease in HCV RNA (IU/mL) from baseline level after 12 weeks of therapy
NR	Null response	Less than 2 $\log_{10}$ decrease in HCV RNA (IU/mL) from baseline after 12 weeks of therapy
LVR or DVR	Late virological response or delayed virological response	More than 2 $\log_{10}$ decrease in HCV RNA (IU/mL) but detectable HCV RNA after 12 weeks of therapy, and undetectable HCV RNA after 24 weeks of therapy
EOTR, ETR, or ETVR	End-of-treatment (virological) response	Non-detectability of HCV RNA at the end of therapy
SVR	Sustained virological response	Undetectable HCV RNA (<50 IU/mL) 24 weeks after the end of therapy
Relapse	Relapse	Undetectable HCV RNA at the end of therapy, but reappearance of HCV RNA after the end of therapy
PR	Partial response or partial nonresponse	More than 2 $\log_{10}$ decrease in HCV RNA (IU/mL) from baseline at 12 weeks of therapy, but detectable HCV RNA at week 24
BT	Breakthrough	Reappearance of HCV RNA at any point during treatment after virological response

infected with these HCV genotypes [138]. Prophylactic interferon is not recommended in needlestick injuries because of low overall infectivity rate [7].

CHC

The objective of antiviral treatment for chronic HCV infection is to prevent liver-related complications, including HCC, by accomplishing SVR [125–132]. Factors associated with SVR are listed in Table 3. Clinical, biochemical, genetic, virological, and therapeutic factors have been shown to influence treatment outcome [139–143].

IL28B SNPs and interferon therapies

Several genome-wide association studies demonstrate that host SNPs near the *IL28B* (interferon lambda 3) gene are associated with SVR to treatment with peginterferon alfa and ribavirin in CHC patients [144–148]. These SNPs are also associated with spontaneous clearance of HCV in acute HCV infection. Although the various distributions of IL28B polymorphisms among different populations worldwide may partly explain the heterogeneity in the responses to interferon-based treatments among different ethnic groups, the biology of these genetic variations is poorly understood. The *IL28B* SNPs are strongly associated with SVR rates in patients who are infected with HCV genotypes 1 or 4 and receive combination treatment with peginterferon alfa and ribavirin. However, the association between *IL28B* variations and treatment response in patients infected with HCV genotypes 2 or 3 is still controversial. *IL28B* variations are associated with very early on-treatment viral kinetics in CHC patients who undergo interferon alfa-based therapy, and are the strongest pretreatment predictor of treatment response in patients infected with HCV genotype 1. *IL28B* variations will continue to influence SVR as long as interferon is included in the antiviral treatment against HCV. However, the impact could be drastically reduced when an interferon-spared regimen becomes available.

Table 3 Factors associated with sustained virological response

Clinical factors
Body mass index, body weight
Age
Gender
Insulin resistance
Coinfection with HBV or HIV
Biochemical and pathological factors
ALT
GGT
Staging of liver fibrosis
Genetic factors
Race: Asian
IL28B (interferon lambda 3)-associated SNPs: favorable genotype
Virological factors
HCV RNA: low viral load (<400,000 IU/mL)
HCV genotype: non-1
HCV genotype 1 core substitutions: 70 wild
HCV genotype 1 NS5A 2209–2248, ISDR mutations: mutant type
HCV genotype 1 NS5A 2334–2379, IRRDR
Therapeutic factors
Adherence to therapy: dose and duration
Rapid virological response
Treatment-naive

ISDR interferon sensitivity-determining region [261], *IRRDR* interferon/ribavirin resistance-determining region [262]

Normal ALT levels

Approximately, 25% of patients with chronic HCV infection have normal ALT levels. Whether or not these patients require treatment remains a matter of controversy. First, we should start from a question of what the normal ALT level is. The conventional definition of a normal ALT level was set in the 1980s based on 95% of a "normal" population that might have included patients with undiagnosed chronic hepatitis or non-alcoholic fatty liver diseases. It is known that a substantial proportion of such individuals have histologically proven liver damage (≥F2) that progresses at approximately 50% of the rate seen in patients with elevated ALT levels. Therefore, some investigators claim that the conventional definition of normal ALT levels should be revised [149–151]. To date, there has been only one randomized controlled trial investigating the efficacy of peginterferon alfa plus ribavirin therapy for patients with persistently normal ALT levels. According to the report, the SVR rates achieved after treatment, in the case of infections with genotypes 1, 2, or 3, were similar among those with normal and abnormal ALT levels. In addition, the ALT level decreased up to 10 IU/L in treated patients and remained low in those with SVR [152, 153].

Patients with no (F0) or minimal (F1) hepatic fibrosis do not necessarily need antiviral therapy. However, they should receive advice concerning the following:

1. Natural history of their disease, especially the likelihood and projected timing of any possible liver-related complications.
2. Efficacy of available treatments.
3. Cost of available treatments.
4. Adverse effects of available treatments, and need for ongoing contraception after administration of ribavirin.

Current standard of care (SOC)

The success rate of HCV treatment has improved further since the last APASL consensus statement in 2007. The combination of once-a-week subcutaneous injection of long-acting peginterferon alfa combined with daily oral ribavirin is the current standard treatment, especially for patients infected with HCV genotype 1 (and 4) [154–159]. The recommended dose of peginterferon alfa-2a is 180 μg weekly and that of peginterferon alfa-2b is 1.5 μg/kg body weight. Ribavirin doses of 1,000 mg daily are recommended for persons weighing up to75 kg and 1,200 mg for persons weighing more than 75 kg [7].

Two forms of peginterferon

There are two licensed peginterferon alfa products available for use: peginterferon alfa-2a and alfa-2b. There are several papers concerning the different efficacies of these two interferons [160–166] (Table 4). A meta-analysis reported that peginterferon alfa-2a was associated with slightly higher SVR rates than peginterferon alfa-2b [166].

Cautions

Prior to starting interferon and ribavirin treatment, special caution should be taken to identify those who might be at high risk of adverse effects [7] (Table 1); monitoring during therapy is recommended mainly to prevent serious adverse events [167].

Special care for interferon and ribavirin treatment includes the following [7].

- Persons who take ribavirin should practice strict contraception during treatment and for 6 months after the termination of treatment.
- Adverse events are usually more severe in the initial weeks of treatment and can often be managed with analgesics and antidepressants.
- Adverse events due to ribavirin and interferon can be controlled by erythropoietin and granulocyte colony stimulating factor (GCSF).

Patients infected with HCV genotypes 2 and 3 had SVR rates over 80% [18, 168–174]. It is recommended that patients infected with HCV genotype 1 be treated for 1 year and that those infected with genotypes 2 or 3 be treated for 6 months. Recent data suggest that 72 weeks of therapy may be more efficacious than 48 weeks of therapy in genotype 1 (and 4) patients with delayed response to interferon/ribavirin therapy (Table 5). As the number of patients with such delayed responses is small, some future large-scale studies will be required before a definite conclusion can be drawn [175–178]. A correlation between the responses and rate of SVR has been reported and may be useful for deciding treatment duration.

Adjuvant or complementary therapy for chronic HCV infection

Patients who do not achieve an SVR include those who have a primary null response and those who relapse. Here, we describe adjuvant or complementary therapy for patients who are null responders of current SOC, peginterferon plus ribavirin therapy, and for patients in whom such therapy is contraindicated. Apart from interferon alfa-based therapies, some comment needs to be made about the use of complementary therapies as they are in wide use in the Asia-Pacific region [179–185]. No proposed adjuvant or complementary therapy has been shown to improve SVR or to decrease hepatic fibrosis [7]. However, therapies that have been proven to reduce serum ALT might be considered in the absence of the effective treatment to achieve SVR [7]. Such adjuvant therapies might include phlebotomy, ursodeoxycholic acid (UDCA), and Stronger Neo-Minophagen C (SNMC), a glycyrrhizin [7]. In patients who fail to respond to interferon treatment, or those in whom interferon therapy is contraindicated, adjuvant therapies might be useful. Recently, the effect of a daily dose of 600 mg UDCA was proven to decrease ALT and G-GTP levels in patients in RCT. Ofloxacin, non-steroidal anti-inflammatory drugs, and amantadine (or its analogs) have been found to be not beneficial. Thymosin alfa-1, peptide vaccine, and cyclophilin inhibitor Debio 025 have shown

Table 4 Comparison of the outcomes of treatment with peginterferon alfa-2a plus ribavirin versus peginterferon alfa-2b plus ribavirin

Authors [ref.]	SVR rates PEG-IFN alfa-2a versus PEG-IFN alfa-2b	*p* values
Laguno et al. [161]	32% versus 28%	NS
McHutchison et al. [162]	41% versus 40%, 38%	NS
Rumi et al. [163]	48% versus 32%	0.04
Ascion et al. [164]	55% versus 40%	0.04
Witthoeft et al. [165]	50% versus 44%	0.047
Award et al. [166]	47% versus 41%	0.004

SVR sustained virological response, *PEG-IFN* peginterferon, *NS* not significant

Table 5 Comparison of the effects of 48 weeks and 72 weeks of therapy

Authors [ref.]	SVR to 48-week Tx	SVR to 72-week Tx	*p* values
Berg et al. [175]			
EVR	104/130 (80%)	90/119 (76%)	NS
Non-EVR	17/100 (17%)	31/106 (29%)	0.04
Total	121/230 (63%)	121/225 (54%)	NS
Pearlman et al. [176]			
LVR	9/49 (18%)	20/52 (38%)	0.026
Ferenci et al. [177]			
cEVR	56/87 (64.4%)	68/93 (73.1%)	NS
pEVR	15/52 (28.8%)	20/57 (35.1%)	NS
Buti et al. [178]			
LVR	37/86 (43%)	35/73 (48%)	NS

SVR sustained virological response, *Tx* therapy, *EVR* early virological response, *LVR* late virological response, *cEVR* complete EVR, *pEVR* partial EVR, *NS* not significant

some promise, alone or in combination with interferon alfa, but larger studies are required.

Patients should be monitored for hepatic, renal, or pulmonary toxicity during treatment with herbal medicines, when administered alone and especially when administered in combination with antiviral therapy [7]. In patients with a non-response to interferon or combination interferon/ribavirin therapy, vitamin E, statins, thymosin alfa l, interleukin-10, UDCA, TJ-9 (Sho-saiko-to), glycyrrhizin, and possibly other herbal medicines such as silymarin or silibinin might be worthy of further evaluation for their effects on hepatic fibrosis and risk of HCC development.

Maintenance therapy with interferon

There is some evidence that maintenance therapy with low-dose interferon or peginterferon might have secondary benefits of reducing inflammation and fibrosis progression and possibly delaying the development of HCC. However, the value of maintenance therapy is still controversial and needs further studies. At this moment, peginterferon maintenance therapy is not universally recommended to CHC patients who do not respond to standard therapy, although some selected patients may benefit from it [112, 186–188]. The Hepatitis C Antiviral Long-term Treatment against Cirrhosis (HALT-C) trial showed that long-term therapy with peginterferon alfa-2a did not reduce the rate of disease progression in patients with CHC and advanced fibrosis, who did not respond to initial treatment with peginterferon and ribavirin [186]. However, it showed that patients with cirrhosis who received peginterferon treatment had a lower risk of HCC than controls [187]. Another large-scale randomized controlled trial with peginterferon alfa-2b that enrolled more than 600 patients with compensated cirrhosis failed to prove the beneficial effect of low-dose peginterferon on the reduction of clinical events, although subgroup analysis of patients with baseline portal hypertension revealed a statistically significant difference between treated patients and controls [188]. Similar studies may be needed in Asia.

Retreatment of CHC patients who fail to achieve SVR

In CHC patients, retreatment with peginterferon alfa and ribavirin combination therapy (SOC) could achieve SVR in only 10–15% of non-responders and 40–50% of SVR in relapsers [189–195]. Although relapsers who have factors favorably associated with SVR may be retreated with peginterferon plus ribavirin without the addition of directly acting antiviral agents (DAAs), in the near future, triple therapy with DAAs should be the standard therapy for retreating CHC patients who fail to respond to SOC [26, 196–198].

Treatment of infection with other HCV genotypes

Genotype 4

The recommended duration of therapy for patients infected with HCV genotype 4 is 48 weeks. Variable duration of treatment with peginterferon alfa-2b and ribavirin confirmed that 48 weeks of therapy was superior to 36 and 24 weeks of treatment. It was believed that genotype 4 patients without early virological response (EVR) do not achieve SVR and hence would not benefit from continuing therapy. However, in another trial, EVR showed a low negative predictive value in predicting failure to achieve SVR. Ferenci et al. [199] observed SVR in 26/30 genotype 4 patients with rapid virological response (RVR) (87%) after 24 weeks of treatment with peginterferon alfa-2a and ribavirin.

In general, genotype 4 patients should receive combination therapy with peginterferon alfa (standard dosage) and high, weight-based dose of ribavirin (1,000–1,200 mg/day) for 48 weeks. There is insufficient data to support alternative treatment regimens at this stage [199–201].

Genotype 5

HCV genotype 5 infection has been reported in South Africa, where it is the most prevalent genotype. As there is not enough data available to suggest optimal treatment, it is recommended that these patients receive the same treatment as genotype 1 patients [202–204].

Genotype 6

It was reported that Vietnam and Thailand have genotype 6 patients with prevalence figures of 6 and 30%, respectively. SVR rates of 75 and 86% have been reported in small studies. Compared to a standard 48-week schedule, therapy for 24 weeks was associated with lower SVR rate (39 vs. 75%, $p = 0.044$). Therefore, it is currently recommended that subjects with HCV genotype 6 infection should be treated like genotype 1 and 5 patients [205, 206]. However, a prospective randomized trial has reported similar SVR rates in HCV genotype 6 patients treated for 24 (70%) and 48 (79%) weeks with peginterferon and ribavirin [207]. These studies were small-scale trials, and further larger prospective studies for HCV genotype 6 patients are needed to confirm the optimal regimen.

New drugs for HCV: protease inhibitors and others

Although current SOC with peginterferon plus ribavirin therapy can cure a significant proportion of patients with chronic HCV infection, the therapeutic efficacy is still not satisfactory, especially for HCV genotype 1 patients with unfavorable genetic variations related to the *IL28B* gene and on-treatment viral kinetics. In addition, peginterferon plus ribavirin therapy is prolonged, costly, and associated with many unpleasant side effects. Therefore, more effective, tolerable, and tailored regimens are semi-urgently required to cure more patients with chronic HCV infection. New, specifically targeted antiviral therapy for hepatitis C (STAT-C) drugs or DAAs have been developed to improve the virological response rates to current SOC and may shorten the duration of therapy.

Telaprevir (phase III): treatment-naïve HCV genotype 1 patients

After phase II trials [208, 209], two phase III clinical trials (ILLUMINATE and ADVANCE) have now been published [197, 210, 211]. The ILLUMINATE trial ($n = 540$) was a randomized, open-label study to evaluate 12 weeks of telaprevir in combination with 24 or 48 weeks of peginterferon alfa-2a plus ribavirin in patients with extended RVR (eRVR), defined as undetectable HCV RNA at weeks 4 and 12 of therapy. Patients who did not achieve eRVR were assigned to receive 12 weeks of telaprevir in combination with 48 weeks of peginterferon alfa-2a plus ribavirin (Fig. 1). In brief, 72% patients ($n = 389$) achieved RVR, and 65% ($n = 352$) achieved eRVR. The overall SVR rate was 72%. In patients who achieved eRVR, the SVR rates in those who received 24 and 48 weeks of therapy were 92 and 88%, respectively. Treatment was discontinued in 36 (7%) and 94 (17%) patients because of virological failure and adverse events, respectively. The most common adverse events leading to premature treatment discontinuation were fatigue and anemia. In summary, the SVR rate in patients with eRVR who received 24 weeks of treatment was similar to that in those who received 48 weeks of treatment. Adding telaprevir to SOC might improve RVR rate, and response-guided therapy led to an SVR rate of 72%.

The ADVANCE trial was a randomized, double-blind, placebo-controlled study to assess the efficacy and safety of 8 or 12 weeks of telaprevir treatment in combination with peginterferon alfa-2a plus ribavirin for 24 weeks in patients who achieved eRVR or 48 weeks in patients who failed to achieve eRVR. The 8- and 12-week telaprevir arms had higher RVR rates than the SOC arm (66 and 68 vs. 9%). In addition, the SVR rates during response-guided therapy were significantly higher in the 8- and 12-week telaprevir arms than in the SOC arm (69 and 75 vs. 44%, $p < 0.001$). A total of 7% and 8% of patients in the telaprevir arms discontinued treatment due to adverse events, compared to 4% in the SOC arm. The most common adverse events were pruritus and anemia. In summary,

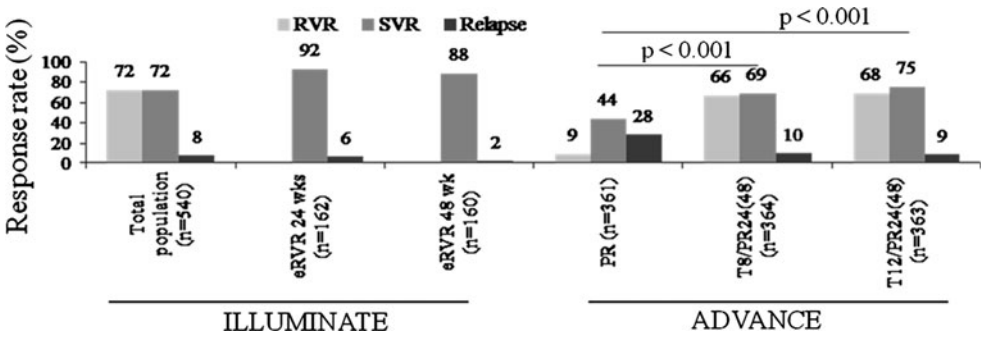

Fig. 1 Final results of phase III ILLUMINATE and ADVANCE trials in treatment-naïve HCV genotype 1 patients. *P* peginterferon, *R* ribavirin, *T* telaprevir, *eRVR* extended rapid virological response. Ref. [197, 210, 211]

either 8 or 12 weeks of telaprevir-based therapy could improve RVR, and response-guided therapy could maintain high SVR rates and avoid overtreatment.

Telaprevir (phase III): treatment-experienced HCV genotype 1 patients

After a phase II trial [212], the REALIZE trial ($n = 662$) was conducted, a randomized, double-blind, placebo-controlled phase III study for treatment-experienced HCV genotype 1 patients with 12 weeks of telaprevir in combination with 48 weeks of peginterferon alfa-2a and ribavirin [198] (Fig. 2). One arm of a 4-week lead-in phase of peginterferon alfa-2a and ribavirin before the use of telaprevir was included to evaluate if the SVR rate would be improved, compared to the other arm of simultaneous use at the start of therapy. The SVR rates in the lead-in and add-on telaprevir arms were similar in both arms and in all subgroups of patients. Compared to the SOC arm, add-on telaprevir significantly improved the SVR rates in all patients (66 and 64 vs. 17%), prior relapsers (88 and 83 vs. 24%), prior partial responders (54 and 59 vs. 15%), and prior non-responders (33 and 29 vs. 5%) ($p < 0.001$). In summary, in treatment-experienced HCV genotype 1 patients, the SVR rate was higher in patients treated with telaprevir for 12 weeks in combination with 48 weeks of SOC than in those treated with SOC. The lead-in phase of peginterferon alfa-2a and ribavirin before telaprevir did not have additional therapeutic benefit.

Boceprevir (phase III): treatment-naïve HCV genotype 1 patients

After a phase II trial [213], the SPRINT-2 trial ($n = 1097$, 938 non-Black and 159 Black patients) was conducted, a randomized, double-blind, placebo-controlled phase III international study for treatment-naïve HCV genotype 1 patients [196] (Fig. 3). All patients received a 4-week lead-in treatment of peginterferon alfa-2b and ribavirin, followed by randomization to (1) 44 weeks of boceprevir with SOC, (2) 44 weeks of SOC, and (3) 24 weeks of response-guided therapy with boceprevir and SOC, and additional 20 weeks of SOC when serum HCV RNA level was detectable during weeks 8–24. The SVR rates in non-blacks who received response-guided or non-response-guided boceprevir treatment were significantly higher than the rates in those who received SOC (68 and 67 vs. 40%, $p < 0.0001$). The corresponding SVR rates in Blacks were 42% ($p = 0.044$ vs. control), 53% ($p = 0.004$ vs. control), and 23%. In summary, boceprevir in combination with

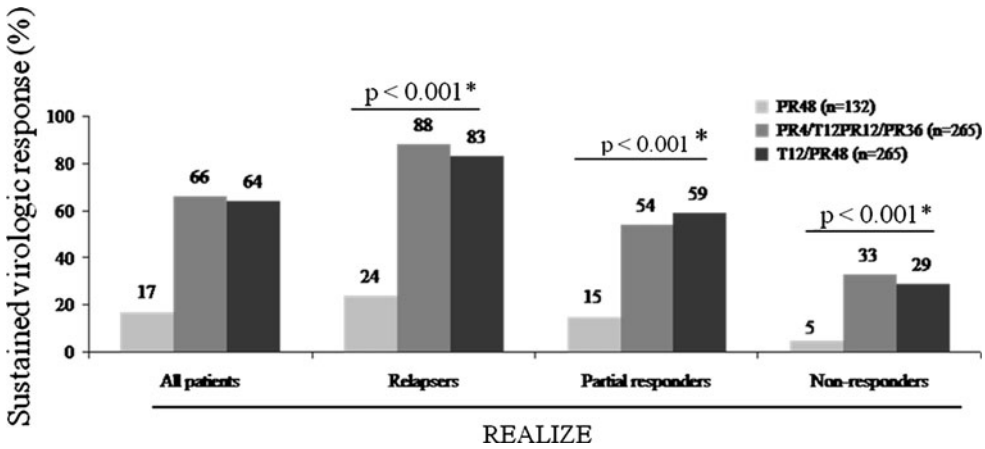

Fig. 2 Final results of phase III REALIZE trials in treatment-experienced HCV genotype 1 patients. *P* peginterferon, *R* ribavirin, *T* telaprevir. *Pooled data of telaprevir lead-in or add-on arms versus control arm. Ref. [198]

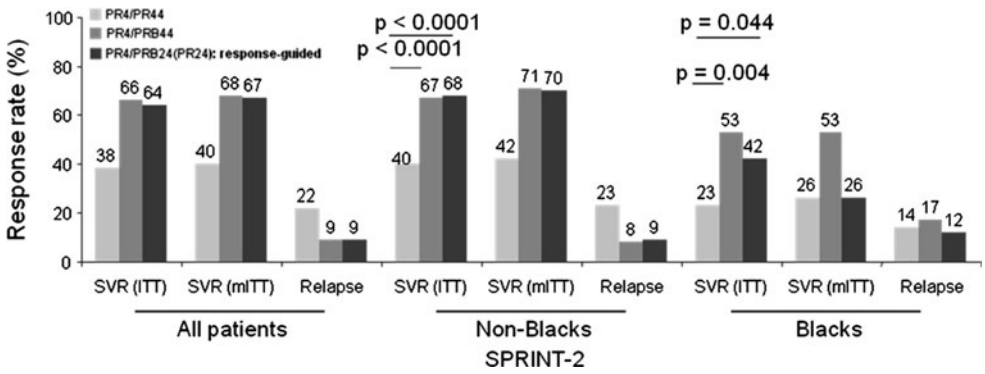

Fig. 3 Final results of phase III SPRINT-2 trials in treatment-naïve HCV genotype 1 patients. *P* peginterferon, *R* ribavirin, *B* boceprevir, *SVR* sustained virological response, *ITT* intention-to-treat, *mITT* modified intention-to-treat. Ref. [196]

peginterferon alfa-2b plus ribavirin improved the overall SVR rate in both non-blacks and blacks. Although anemia occurred more frequently in patients treated with boceprevir, it rarely led to treatment discontinuation. The SVR rates were comparable in patients treated with response-guided or non-response-guided boceprevir therapy.

Boceprevir (phase III): treatment-experienced HCV genotype 1 patients

The RESPOND-2 trial ($n = 403$) was a randomized, double-blind, placebo-controlled phase III international study for treatment-experienced HCV genotype 1 patients (Fig. 4) [26]. All patients received a 4-week lead-in treatment with peginterferon alfa-2b plus ribavirin, followed by randomization to (1) 44 weeks of boceprevir with SOC, (2) 44 weeks of SOC, and (3) 32 weeks of response-guided therapy with boceprevir and SOC, and an additional 12 weeks of SOC when serum HCV RNA level was detectable at week 8, but became undetectable at week 12 of treatment (Fig. 4). A total of 35–36% of the study population were prior non-responders, and the others were prior relapsers. The SVR rates in the response-guided (59%) and non-response-guided (66%) boceprevir treatment arms were higher than that in the SOC arm (21%) ($p < 0.0001$). The SVR rates during response-guided boceprevir treatment, non-response-guided boceprevir treatment, and SOC were 40, 52, and 7%, respectively, in prior non-responders and 69, 75, and 29%, respectively, in prior relapsers. The relapse rates were lower in patients treated with boceprevir (15 and 12%) than in patients treated with SOC (32%). In summary, in treatment-experienced HCV genotype 1 patients, boceprevir in combination with peginterferon alfa-2b and ribavirin improved the overall SVR rates both in prior non-responders and relapsers.

Future perspectives in Asian CHC patients

By using the genome-wide association study (GWAS), host *IL28B* genetic polymorphisms, encoding interferon-λ-3 on chromosome 19, have shown to be associated with treatment responses in European, African-American, and Asian CHC patients with HCV genotype 1 infection. The higher SVR rates during SOC in Asian patients than in Western patients (70 vs. 50%) may be partly explained by the fact that Asian patients have a higher frequency of favorable *IL28B* gene SNPs than Western patients. With this inherent advantage, Asian treatment-naïve HCV genotype 1 patients treated with 24-week triple therapy with DAA and peginterferon plus ribavirin are expected to have an even higher SVR rate of 90%.

Although DAAs in combination with peginterferon alfa plus ribavirin may improve the treatment responses in HCV genotype 1 patients, the added adverse events and costs may preclude the unselected use of these agents (Table 6). This question is particularly relevant in Asian

Table 6 Common adverse events and resistance-associated HCV variants and therapy with telaprevir and boceprevir

Telaprevir for untreated chronic hepatitis C virus infection [193]		
Adverse event	With telaprevir (%)	Without telaprevir (%)
Gastrointestinal disorders		
Nausea	40–43	31
Diarrhea	28–32	22
Skin disorders		
Pruritus	45–50	36
Rash	35–37	24
Anemia	37–39	19
Boceprevir for untreated chronic hepatitis C virus infection [192]		
Adverse event	With boceprevir (%)	Without boceprevir (%)
Anemia	49	29
Dysgeusia	37–43	18
Neutropenia (500–750/mm^3)	24–25	14
Resistance-associated variants	15–17	–

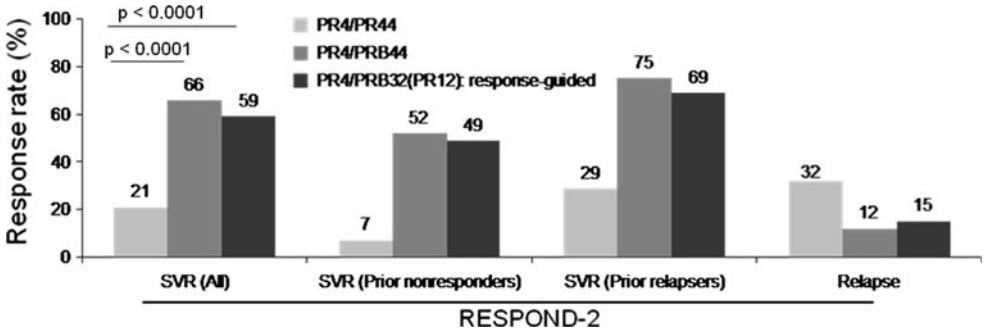

Fig. 4 Final results of phase III RESPOND-2 trials in treatment-experienced HCV genotype 1 patients. *P* peginterferon, *R* ribavirin, *B* boceprevir. Ref. [26]

HCV patients because of the anticipated higher RVR and SVR rates as compared to Western patients. From the Asian perspective, we should focus on the role of *IL28B* genotypes in Asian HCV genotype 1 or 2 patients who can benefit from truncated duration of peginterferon alfa plus ribavirin therapy, or those who can benefit from the additional use of DAAs from further clinical trials. Large-scale studies are required to make individualized therapy more practical for Asian HCV patients and improve therapeutic efficacy and reduce medical expenses in Asia [214].

Furthermore, it seems that there are differences between HCV subtypes 1a and 1b. Drug resistance to telaprevir or boceprevir is more frequently observed with HCV subtype 1a than 1b [215–217]. Various NS5B polymerase non-nucleoside inhibitors (NNIs) have also shown to be less active against HCV subtype 1a than 1b [218]. Of interest, a recent preliminary study of interferon-spared regimens with two DAAs indicated that SVR may differ between subtypes 1a and 1b. Thus, interferon-spared regimens may have a bigger impact on HCV treatment in Asian countries where 90% of HCV genotype 1 infections are accounted for by subtype 1b.

Consensus statements: treatment of HCV infection

Acute HCV infection.

1. Treatment of acute hepatitis C should be delayed for 8–16 weeks to allow for spontaneous resolution, especially in symptomatic patients (II-1). However, patients with an unfavorable *IL28B* genotype can be offered treatment earlier than 12 weeks, as the chances of spontaneous resolution of infection are low.
2. Both standard interferon (high dose) and peginterferon can be used for treating subjects with acute hepatitis C (I).
3. Treatment of acute HCV infection should be continued for 24 weeks in the case of genotype 1 and for 12 weeks in the case of genotypes 2 or 3 (II-1).
4. The addition of ribavirin does not appear to increase SVR in patients with acute hepatitis C treated with either interferon or peginterferon (II-2).
5. Patients with active drug use and HCV/HIV coinfection can be usefully treated with peginterferon for 24 weeks.

Chronic HCV infection (treatment with SOC).

6. SVR should be the goal of antiviral therapy for HCV infection. Biochemical (ALT levels) and histological response should be used only as secondary descriptors, although normalization of ALT levels and histological improvement might also modify the natural history and clinical outcomes (II-2).
7. Prior to starting interferon and ribavirin treatment, the following should be completed: (III)
   - Full medical history and clinical examination.
   - Baseline laboratory tests including liver biochemistry, renal function, complete blood count, thyroid function, and auto-antibody studies.
   - Serum HCV RNA (quantitative) and HCV genotyping/serotyping.
   - Liver biopsy, if appropriate.
   - Cardiac and pulmonary evaluation, if indicated.
   - Psychiatric evaluation, if indicated.
   - Pregnancy test.
8. The conventional definition of normal ALT levels includes a substantial proportion of patients with liver fibrosis. Patients with normal ALT levels have response rates similar to those with raised ALT levels and could be considered for therapy, especially when liver biopsy shows moderate to advanced fibrosis, their ALT level is close to the upper limit, and the expected SVR rate is high (I).
9. Patients with HCV genotype 2 and 3 can be treated regardless of the stage of the disease (III).
10. Patients with compensated cirrhosis, but not decompensated cirrhosis, can be considered for treatment (I).
11. During treatment, the following should be performed: (III)
    - Full medical history and clinical examination at every visit.
    - Liver biochemistry and renal function every 4 weeks.
    - Complete blood count at 2, 4, and 6 weeks and every 4 weeks thereafter.
    - Serum HCV RNA testing at 4 and 12 weeks.
    - Thyroid function every 3–6 months.
    - Psychiatric evaluation, if indicated.
    - Chest X-ray, ophthalmic or audiogram examination, if indicated.
    - Cardiac assessment, if indicated.
    - Reinforcement of advice regarding need for contraception.
12. In chronic HCV genotype 1 infection, the following apply: (I)
    - Treatment with peginterferon and ribavirin for 48 weeks is recommended.
    - In patients who achieve an RVR at week 4, treatment can be discontinued after 24 weeks if the HCV RNA at baseline is <400,000 IU/mL.

- In patients who achieve a complete EVR at week 12, treatment should be continued up to 48 weeks.
- In patients who do not achieve an EVR at week 12, but show a significant reduction in HCV RNA levels (partial EVR) and negativity of HCV RNA at week 24 (late virological response, LVR), treatment may be continued up to 72 weeks (Fig. 5).

13. In chronic HCV genotype 2 or 3 infection, the following apply: (I)

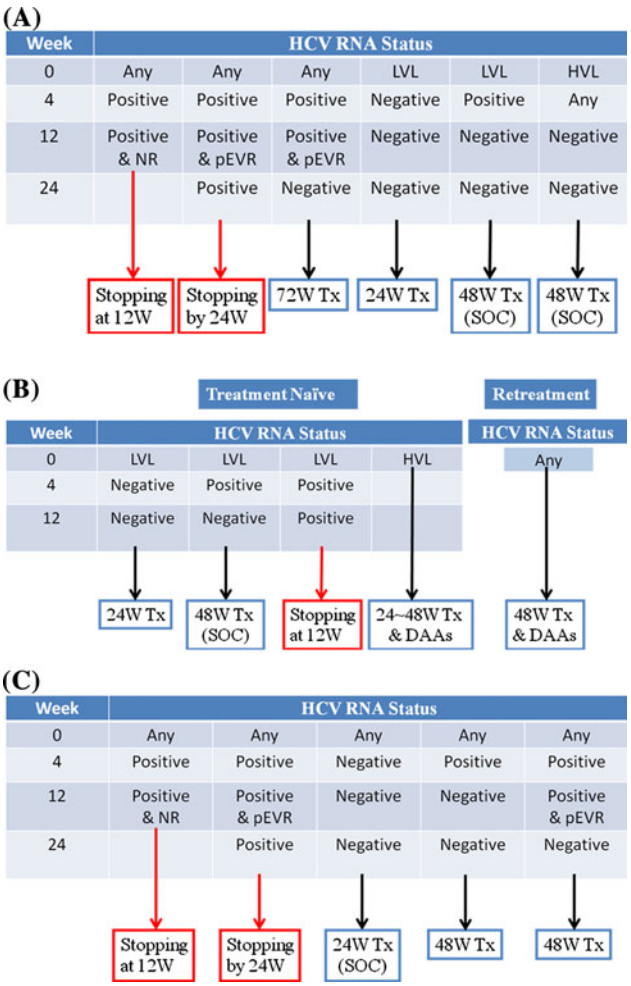

Fig. 5 An algorithm can provide some direction regarding treatment of chronic hepatitis C caused by HCV genotype 1 (**a**, **b**) and non-genotype 1 (**c**). **a** Treatment of patients with HCV genotype 1 by peginterferon plus ribavirin. **b** Treatment of patients with HCV genotype 1 by direct-acting antivirals (DAAs) plus peginterferon with ribavirin. Selection of regimen and on-treatment stopping rules with telaprevir are different from those of boceprevir. **c** Treatment of patients with HCV-non-genotype 1 by peginterferon plus ribavirin. *HVL* high viral load, *LVL* low viral load; *Any* HVL and LVL, *pEVR* partial early virological response, *Positive* positive for HCV RNA, *Negative* negative for HCV RNA, *NR* null response, *SOC* standard of care, *Tx* therapy

- Treatment with either conventional interferon alfa plus ribavirin or peginterferon alfa with or without ribavirin for 24 weeks is recommended (although peginterferon plus ribavirin might be more effective in patients with cirrhosis or a high viral load).
- There is some evidence that shortening duration of therapy to 16 weeks in patients with HCV genotype 2 infection provides equal SVR to 24 weeks of treatment (Fig. 5).

14. After treatment: (III)

- If end-of-treatment virological response (ETVR) is achieved, the patient should be followed up and serum HCV RNA levels should be reassessed 24 weeks later to document SVR.
- Effective birth control should be continued for at least 6 months after the end of treatment with ribavirin.

15. In those who have undergone previous treatment with conventional interferon or peginterferon monotherapy and experienced non-response or relapse, retreatment with peginterferon plus ribavirin can be considered, particularly in those with significant fibrosis or cirrhosis (II-2).
16. Peginterferon maintenance therapy is not universally recommended to CHC patients who do not respond to standard therapy (I).

Chronic HCV genotype 1 infection (treatment with DAAs).

17. This applies only to countries where telaprevir and boceprevir are available. Telaprevir in combination with peginterferon alfa plus ribavirin significantly improves SVR rates in treatment-naïve and treatment-experienced HCV 1-infected patients.
18. Boceprevir in combination with peginterferon alfa plus ribavirin significantly improves SVR rates in treatment-naïve and treatment-experienced HCV 1-infected patients (Fig. 5).
19. Grade 3 adverse events (mainly anemia, neutropenia, and leukopenia) are frequent (Table 6). Special caution against skin disorders such as rash, drug eruption, and erythema should be taken at every hospital visit. When skin disorders of grade 2–4 occur, clinicians should consult a dermatologist for the reduction or discontinuation of protease inhibitors [219, 220].

The original guidelines were published in [7]. Points 1, 5, 8, 9, 10, 12, 13, 16, 17, 18, and 19 are revised or new recommendations.

Special groups

HCV infection in liver transplant candidates

Since HCV reinfection after liver transplantation is universal and inevitable, this can be the key factor for premature graft loss. The treatment of HCV infection after liver transplantation potentially induces graft loss due to rejection and is associated with reduced efficacy owing to the concomitant use of immunosuppressive agents. Because of these reasons, treatment of CHC in liver transplant candidates with HCV-induced cirrhosis draws much attention [7, 221–223].

Many retrospective, non-randomized studies indicate that there is a high risk of infection in patients with HCV-induced cirrhosis, especially in those with decompensated cirrhosis who have been treated with interferon and ribavirin.

A retrospective randomized controlled trial of peginterferon alfa-2a plus ribavirin therapy for HCV-infected cirrhotic patients awaiting liver transplantation in Spain showed higher incidence of bacterial infection in treated patients versus controls. This was particularly the case in individuals with Child–Pugh grades B or C, with two patients dying of spontaneous bacterial peritonitis (SBP) and pneumonia. Acute liver failure and bone marrow suppression were also more common in the treatment arms. Overall, 20% SVR rates were achieved, with more successful outcomes in patients with EVR and those with genotype non-1 infections. Norfloxacin prophylaxis for SBP is recommended in patients with poor liver function.

Consensus statements: HCV infection and liver transplantation

1. Patients with decompensated hepatitis C can be considered for antiviral treatment, provided they have a Child–Pugh score $\leq$7 and a MELD score $\leq$18 with a platelet count >60,000. Patients should be monitored closely by an experienced liver unit. A low ascending dose regimen should be adopted, and supportive therapies to prevent variceal bleeding and infections, and correct cytopenias are recommended. (II-2)
2. In hepatitis C patients being considered for liver transplantation, the minimal listing criteria should be identical to those for other primary liver diseases (II-2).
3. Following liver transplantation, pre-emptive treatment for recurrent hepatitis C (<6 months after transplant) should only be administered within clinical trials (II-2).
4. Treatment of established recurrence (>6 months after transplant) should be considered in those with severe disease. The preferred regimen is at least 48 weeks peginterferon plus ribavirin (I).
5. Over-immunosuppression should be avoided in the early post-transplant period (II-2).
6. Rapid steroid withdrawal should also be avoided in the later post-transplant period (III).

The original guidelines were published in [7]. The above list does not include any new recommendations.

HCV infection in chronic kidney disease

Comorbidities of HCV infection and chronic kidney disease (CKD) might present in two ways: HCV infection during maintenance dialysis and HCV-associated kidney disease. These disorders can occur both in native kidneys and in renal allografts; in particular, membranous nephropathy occurs in most renal allografts. Therefore, all patients with kidney diseases should be evaluated for possible underlying HCV infection. It is suggested that HCV-infected patients be tested at least annually for proteinuria and hematuria [7, 224, 225].

Among dialysis patients with HCV infection, cirrhosis, Asian race, and history of alcohol abuse are the highest risks for development of HCC [226]. Also, HCV infection is associated with higher risk of liver-related mortality in patients on dialysis, even after adjusting for concurrent comorbidities. Further, the risk remains high over time. Additionally, HCV infection decreases the health-related quality of life in dialysis patients.

HCV RNA is a direct marker of HCV replication. Therefore, sensitive quantitative RT-PCR tests for HCV should be administered to hemodialysis patients with unexplained abnormal aminotransferase(s) levels. Usually, end-stage renal disease (ESRD) patients have lower serum ALT levels than the general population. Some studies suggest that for HCV-infected patients, the optimized cutoff ALT level be approximately 0.4–0.45 times the upper limit of normal.

Combined peginterferon alfa or interferon alfa and ribavirin is still the mainstay of treatment for HCV infection in CKD patients with normal, mild, moderate, or severe decrease in the glomerular filtration rate (GFR), and even kidney failure. However, HCV-infected CKD patients with moderate to severe decrease in GFR (15–59 mL/min) and kidney failure should be treated with reduced doses of peginterferon alfa-2a (135 μg/week) or peginterferon alfa-2b (1 μg/kg/week) and ribavirin (200–800 mg/day). For HCV-infected dialysis patients, both standard interferon alfa and reduced doses of peginterferon alfa-2a (135 μg/week) or peginterferon alfa-2b (1 μg/kg/week) monotherapy achieved SVR in <40% patients. Ribavirin can be

used, but at a markedly reduced daily dose with careful monitoring for anemia and other adverse events [227–232].

Kidney transplant candidates should be screened for HCV infection and treated if they test positive for HCV RNA. However, interferon alfa therapies are contraindicated after kidney transplantation owing to potential graft dysfunction or loss, unless the benefits of treatment outweigh the risks, such as in case with fibrosing cholestatic hepatitis.

Consensus statements: HCV and CKD

1. HCV-infected patients should be screened for proteinuria and hematuria at least annually so as to detect HCV-associated kidney disease (III).
2. Maintenance hemodialysis (CKD stage 5D) confers a significant risk of nosocomial infection. Therefore, standard precautions for prevention of nosocomial infections must be rigorously observed (II-2).
3. Patients on hemodialysis should be screened with serological tests and RT-PCR at first hemodialysis or when transferring from another hemodialysis unit. Maintenance hemodialysis patients and kidney transplant candidates should be tested for anti-HCV antibodies every 6–12 months, and RT-PCR should be performed for patients with unexplained elevated aminotransferase(s) (II-2).
4. Regular serological screening of dialysis staff is indicated (II-2).
5. In dialysis patients with chronic HCV infection, liver biopsy is not mandatory, but is recommended especially when the results would influence treatment decisions and when progression of the liver disease needs to be assessed (II-2).
6. SOC is recommended for HCV-infected CKD patients with normal or mild decrease in GFR ($\geq$60 mL/min) (II-2).
7. Reduced doses of peginterferon alfa-2a (135 μg/week) or peginterferon alfa-2b (1 μg/kg/week) and ribavirin (200–800 mg/day) are recommended for HCV-infected CKD patients with moderate to severe decrease in GFR (15–59 mL/min) and kidney failure (<15 mL/min). Standard interferon alfa plus low doses of ribavirin is recommended as well (II-1).
8. Both standard interferon alfa and reduced doses of peginterferon alfa-2a (135 μg/week) or peginterferon alfa-2b (1 μg/kg/week) are recommended for HCV-infected dialysis patients (II-1). Ribavirin should be administered at a markedly reduced daily dose, if combined with interferon (II-3).
9. Interferon alfa therapies are contraindicated in kidney transplant recipients, unless the benefits of the treatment outweigh the risks (II-2). The original guidelines were published in [7]. Points 1, 2, 3, 6, 7, 8 and 9 are revised or new recommendations.

HCV infection in thalassemia and hemophilia

Blood transfusion has historically been one of the main sources of HCV transmission globally [7]. Patients with hemophilia or thalassemia received clotting factor concentrates before 1987 or transfusion before 1993, and were associated with a high prevalence of HCV infection. Moreover, comorbidities of hemophilia or thalassemia and HCV infection lead to higher morbidity and mortality than the original disease [7, 233–236].

The standard treatment of chronic HCV infection in hemophilia or thalassemia patients is combination of peginterferon alfa or interferon alfa and ribavirin, as in general hepatitis C population. According to recently published meta-analysis and systematic review, peginterferon alfa or interferon alfa combined with ribavirin therapy produce similar SVR rates in hemophilia/thalassemia patients and the general HCV-infected population [237, 238]. However, ribavirin-related anemia in thalassaemic patients increases transfusion need by 30–40%, with a transfusion every 3–4 weeks to maintain a hemoglobin level of 9–10 mg/dL [7]. Ribavirin does not increase major adverse events or treatment withdrawal. A prospective, randomized, open-label trial involving peginterferon alfa and ribavirin combination therapy showed a higher SVR rate than peginterferon alfa alone; the former was well tolerated except for an increase in blood transfusion requirement [239]. Genotype 1 infection and coinfection with HIV were strong unfavorable factors for response to interferon therapy.

Consensus statements: HCV infection in thalassemia and hemophilia

1. Patients with thalassemia or hemophilia who have chronic HCV infection should be considered for antiviral treatment (I).
2. In patients with thalassemia or hemophilia, peginterferon monotherapy or combination therapy with ribavirin is recommended, but careful monitoring is needed to detect anemia and other hematologic side effects (I).
3. Following bone marrow transplantation in thalassemia patients, treatment of HCV infection should be considered after immunosuppression therapy has been stopped (II-2).

The original guidelines were published in [7]. Points 1, 2, and 3 are revised or new recommendations.

HCV infection in children

The current upper limit of ALT in children seems too high to reliably detect chronic liver disease. For children with

hepatitis C, biology-based thresholds provide higher sensitivity. Spontaneous virus clearance is very low. A multicenter retrospective/prospective cohort study showed that few children with chronic HCV infection cleared the virus spontaneously over a decade, and that genotype 3 might be a favorable factor for clearance. If spontaneous clearance occurs, it tends to occur early after the infection and at a younger age. Slow fibrotic progression was found in most children with hepatitis C [7, 240–245].

The diagnosis of perinatally acquired HCV infection requires a positive anti-HCV test after 18 months of age or older. RT-PCR for HCV RNA may be considered at 1–2 months of age in infants born to HCV-infected mothers, if early diagnosis is desired [7].

Some studies using a combination of peginterferon alfa-2a or 2b together with ribavirin have shown excellent SVR in the case of genotypes 2 or/and 3 and approximately 57% SVR in the case of genotype 1. The doses of peginterferon alfa have to be modified according to body surface area. Some studies have used ribavirin at a dose of 15 mg/kg/day [246–250].

Consensus statements: HCV infection in children

1. The diagnosis of perinatally acquired HCV requires a positive anti-HCV test after 18 months of age or older. RT-PCR for HCV RNA may be considered at 1–2 months of age in infants born to HCV-infected mothers, if early diagnosis is desired (II-2).
2. Antiviral treatment for hepatitis C can be administered to children between 2 and 17 years of age (II-2).
3. Antiviral response rates in children to peginterferon alfa and ribavirin are similar to those in adults. The doses of peginterferon alfa have to be modified according to body surface area (II-2).

The original guidelines were published in [7]. Point 1 is not included in the original guideline.

HCV and HIV coinfection

Hepatitis C has a limited impact on HIV disease progression. Conversely, HIV alters the natural history of hepatitis C in several important areas [7]. SVR rates following peginterferon and ribavirin therapy in HIV/HCV coinfected patients are 15–20% lower than those in patients with HCV monoinfection [7], but predictors of treatment response are largely factors related to hepatitis C: rapid virological response (RVR), HCV genotype, HCV viral load, *IL28B* gene variation, and liver disease stage [7, 251–256]. SVR to peginterferon alfa and ribavirin reduces liver-related complications and mortality in HCV/HIV coinfected patients. Rates of hepatic decompensation during hepatitis C treatment are considerably higher in coinfected patients than in HCV monoinfected patients, especially among cirrhotics.

Consensus statements: HCV and HIV coinfection

1. Routine screening for HIV is recommended in patients with hepatitis C following exposure risk assessment and pretest counseling.
2. HIV/HCV coinfected patients with advanced HIV disease (CD4 count <100/μL) should receive highly active anti-retroviral therapy (HAART) with HCV treatment delayed until immune function is improved, preferably until a CD4 count >200/μL is achieved (I).
3. Antiretroviral therapy-naïve HIV/HCV coinfected patients with a CD4 count of 100–350/μL should commence HAART prior to HCV treatment (I).
4. HIV/HCV coinfected patients with a CD4 count >350/μL should be considered for HCV treatment and do not require HAART (I).
5. Peginterferon and ribavirin combination therapy for 48 weeks is the recommended HCV treatment; weight-based ribavirin dosing should be considered for HCV genotype 1 patients (I).
6. Undetectable HCV RNA at week 4 of treatment is the best predictor of SVR in HCV/HIV coinfected patients. Extending peginterferon and ribavirin treatment beyond 48 weeks may not improve the overall treatment outcomes.
7. Deferral of HCV treatment should be considered in HIV/HCV coinfected patients with HCV genotype 1 and high viral load (>800,000 IU/mL) if early liver disease (F0/1) is detected on liver biopsy (I).
8. There is insufficient evidence to support administration of HCV treatment to patients with persistently normal ALT levels, but treatment could be considered in those with moderate or severe fibrosis (II-2).
9. SVR to peginterferon alfa and ribavirin reduces liver-related complications and mortality in HCV/HIV coinfected patients.
10. Didanosine, zidovudine, and stavudin should be avoided if the HCV treatment regimen includes ribavirin.
11. As observed in HCV monoinfection, *IL28B* gene variations may independently predict SVR in HCV/HIV coinfected patients with genotype 1 or non-genotype 1 HCV infection (II-1).

The original guidelines were published in [7]. Points 6, 9, 10, and 11 are revised or new recommendations.

HCV and HBV coinfection

For patients who test positive for both anti-HCV and HBsAg, but have significant levels of serum HBV DNA

and undetectable serum HCV RNA, peginterferon alfa or nucleos(t)ide analogs or both can be used [7]. A recent large-scale study demonstrated that in terms of HCV SVR, HCV genotype-guided therapy with peginterferon and ribavirin is equally effective in patients with HCV monoinfection and in HCV/HBV coinfected patients with significant levels of HCV RNA [257]. Long-term effect of interferon and ribavirin on HBsAg seroclearance was observed in HBV/HCV coinfected patients [258–260].

In HCV/HBV coinfected patients who achieved an SVR with peginterferon alfa and ribavirin treatment, long-term follow-up and monitoring for relapse of HBV infection are recommended.

Consensus statements: HCV and HBV coinfection

1. Routine screening for HBsAg is recommended in patients with chronic HCV infection, especially in IDUs or other high-risk populations.
2. Routine testing for serum HBV DNA is not recommended in HBsAg-negative patients with chronic HCV infection.
3. HCC screening tests, including liver ultrasonography and tests for alpha-fetoprotein levels, are required for coinfected patients.
4. HBV and HCV coinfected patients may be selected for antiviral treatment by the same criteria as those used for patients with monoinfection.
5. It is helpful to determine which virus is dominant in patients with dual infection before commencing treatment.
6. In patients who are anti-HCV, HBsAg, and HCV PCR positive, peginterferon alfa combined with ribavirin, 48 weeks for HCV genotype 1 and 24 weeks for HCV genotype 2 or 3, is recommended.
7. For patients who test positive for both anti-HCV and HBsAg, but have significant levels of serum HBV DNA and undetectable serum HCV RNA, peg-IFN alfa or nucleos(t)ide analogs or both can be used.
8. In HCV/HBV coinfected patients who achieve an SVR with peginterferon alfa and ribavirin treatment, long-term follow-up and monitoring for relapse of HBV infection are recommended.
9. HBV vaccination should be offered for hepatitis C patients who are HBsAg negative.

The original guidelines were published in [7]. Points 5, 6, 7, and 8 are revised or new recommendations.

HCV infection and extrahepatic manifestations

Certain patients with chronic HCV infection may suffer from extrahepatic illnesses, with a symptomatic spectrum varying from fatigue to permanent organ damage [7]. In many patients, these illnesses resolve following an SVR with antiviral treatment. Lately, a more than twofold increase in risk for intrahepatic cholangiocarcinoma, as well as some intriguing association of atherosclerosis and metabolic risk factors with chronic HCV infection, has been described.

Consensus statements: HCV infection and extrahepatic manifestations

1. Patients with symptomatic mixed cryoglobulinemia, glomerulonephritis, neuropathy, or vasculitis should be screened for HCV infection and considered for standard antiviral treatment if positive (II-2).
2. Patients with glomerulonephritis and impaired renal function (GFR <50 mL/min) should be treated with interferon monotherapy (II-2).
3. Patients with low-grade B-cell non-Hodgkin's lymphoma, mucosa-associated lymphoid tissue (MALT) lymphoma, and splenic lymphoma should be screened for HCV infection as antiviral therapy might induce remission (II-2).
4. Patients with life-threatening vasculitis and organ failure can be considered for anti-B-cell therapy.

The original guidelines were published in [7]. "HCV infection in children" does not include any new recommendations.

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