SPECIAL REPORT

Asian Pacific Association for the Study of the Liver consensus statements on the diagnosis, management and treatment of hepatitis C virus infection

Asian Pacific Association for the Study of the Liver (APASL) Hepatitis C Working Party

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1. Laboratory testing for HCV infection1-8

Past exposure to hepatitis C virus (HCV) is mostly determined by testing for specific antibodies using an approved enzyme immunoassay (EIA). The presence of antibody shows that the patient has been infected with the virus but does not indicate whether the infection is acute, chronic or resolved. The absence of antibody usually shows that the patient has not been infected. However, antibody might not be detectable in the first few weeks after initial infection (known as the window period) or in patients who are immunosuppressed. Furthermore, there is some evidence that in patients who resolve their infection, antibody levels might decrease and become undetectable many years later.

Several countries in the Asia–Pacific region have developed their own individual testing algorithms for anti-HCV testing. For confirmatory testing, some of these approaches include:

- Repeat testing of reactive samples in the same EIA
- Retesting reactive samples in a second, independent EIA
- Testing by immunoblot
- Presumption that a high signal-to-cut-off ratio for a sample in a specific EIA is highly predictive of an authentic anti-HCV positive result
- Use of a nucleic acid test (NAT) for detection of HCV RNA. Note that although a NAT for HCV RNA can be helpful in diagnosis, it cannot be considered a true confirmatory test.

Ideally, all samples shown to be anti-HCV reactive should be retested using an assay with high specificity to confirm reactivity. However, for some laboratories financial constraints can preclude this approach.

Anti-HCV testing is important for determining exposure to the virus but does not identify whether the patient has current infection. However, this information can be provided by an
appropriately performed NAT for HCV RNA. Qualitative testing for HCV RNA can offer some important advantages, including:

- Determination of chronicity
- Monitoring response to antiviral therapy
- Assessment of anti-HCV indeterminate samples.

Testing for the presence of HCV RNA should be strongly considered in patients at high risk of infection but who might be anti-HCV negative or indeterminate because of immunosuppression (by therapy or disease, such as patients on hemodialysis or with HIV infection). HCV RNA isolation is also necessary for determination of HCV genotypes. A number of HCV genotype classification schemes have been used. In the most recent, HCV has been classified into six major genotypes, which can be further divided into subtypes. Some genotypes such as HCV 1, 2 and 3 are widely distributed, although others are more geographically restricted.

Interferon (IFN)-based therapy has become the mainstay of chronic HCV treatment and improved outcomes have been achieved as knowledge is gained about the predictors of response to therapy. Virus genotype and viral load have been shown to be key viral characteristics to guide treatment and clinical management of patients with chronic infection.

Several methods are available to determine HCV genotype. The method used will vary from country-to-country and might depend on approval by relevant health authorities and/or available funding. Methods include:

- Direct sequencing of PCR product (region amplified could be 5′ untranslated region (UTR), core, NS5A and NS5B)
- Reverse-phase hybridization (e.g. line probe assay)
- Type-specific PCR
- Restriction fragment length polymorphism after PCR amplification
- Melting curve analysis after real-time PCR amplification
- Typing using genotype-specific antibodies
- Restriction fragment mass polymorphism analysis by mass spectrometry.

The 5′ UTR is well conserved but has sufficient nucleotide sequence divergence to discriminate between most genotypes. It is the target region for most diagnostic HCV RNA PCR assays and genotyping based on the 5′ UTR has a high concordance with genotype determined by sequencing of NS5B. A possible disadvantage of relying on the 5′ UTR for genotype determination is its inability to discriminate the HCV genotype 6c-l, highly prevalent in the Asia–Pacific region, which can be mistyped as HCV genotype 1/1b because of sequence homology. Sequence analysis of the core region is sufficient to identify the HCV genotype 6c-l and a new generation line probe assay designed with core-specific oligonucleotides is also being evaluated. At present, the inability to distinguish HCV genotype 6c-l might impact on predicted sustained virological response (SVR) in patients with apparent genotype 1/1b who are to receive IFN-based therapies. Currently trials are underway to evaluate optimal treatment duration for genotype 6.

The final use of HCV RNA isolation is that of viral load estimation. There does not appear to be any association between disease activity, progression to chronicity and HCV viral load. However, viral load has been shown to be a prognostic indicator of therapy outcome. Monitoring of viral load on therapy has also proven useful, especially for patients infected with HCV genotype 1, with the lack of an early virological response predictive of long-term treatment failure. HCV load testing for patients infected with HCV genotypes 2 or 3 is not recommended as nearly all have an early virological response and a qualitative NAT for HCV RNA is preferred.

Commercial signal amplification and target amplification assays are available for quantification of HCV RNA. In addition, several laboratories have developed their own in-house load assays. Traditional end-point PCR for viral load has several disadvantages, in particular a limited dynamic range, so laboratories persisting with in-house testing should adopt the real-time PCR format. Such assays can be calibrated to the World Health Organization (WHO) International Standard.

Most recently, commercial HCV core antigen assays have become available. In some circumstances these might be an alternative to HCV RNA assays. The HCV core antigen assays show a good correlation with HCV RNA assays but due to limited sensitivity, they are probably not suited to the monitoring of patients on therapy. The major role these assays might play is in the identification of blood donors in the seroconversion window.

### Consensus statements: HCV infection and laboratory testing

1. Anti-HCV antibody testing should be by approved anti-HCV third or fourth generation EIA. (II-2)*
2. Samples negative in an approved EIA can be reported as anti-HCV negative. However, it should be noted that individuals on hemodialysis or coinfeected 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-cut-off 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 cut-off, a qualitative NAT for HCV RNA should be considered and/or a further follow-up sample be obtained for both anti-HCV and HCV RNA NAT. (III)
5. HCV RNA qualitative and quantitative testing requires appropriate contamination controls. (II-2)
6. A dedicated sample/aliquot not derived from other test samples is preferred for HCV RNA qualitative and quantitative (viral load) testing. (II-2)
7. HCV RNA quantitation should be reported in IU/mL (optional to include copies/mL).* ** (III)
8. HCV genotype testing is important for assessing treatment duration and efficacy of antiviral therapy. However, it should be recognized that genotype discrimination based on primers from the 5′ UTR do not distinguish some of the genotype 6 subtypes prevalent in South-East Asia and instead classifies them as genotype 1 or 1b. (II-2)
9. Participation in an external quality assurance program for all testing is ideal. (II-2)
10. Internal quality assurance testing is required for all testing. (II-2)

*Numbers in parentheses refer to levels of evidence. An option, which can be used as an alternative to a secondary confirmatory assay, is to use the initial screening assay signal-to-cut-off ratio (S/CO) to estimate the probability of a patient’s true antibody status. The ratio is calculated by dividing the optical density (OD) value of the test sample by the OD of the assay cut-off. An example of the calculation of the ratio:

Sample OD = 2.991, cut-off OD = 0.377, therefore S/CO ratio = 7.934. For most standard EIAs (i.e. those that do not use chemiluminescence), an S/CO ratio greater than 3–4 should be indicative of the presence of true anti-HCV antibodies. Such tests include:

- Murex Anti-HCV (version 4.0)
It has been recommended that for recycling of equipment (e.g. test-tube racks) and for cycler in the amplification area. Aliquotting of reagents both in the PCR reagent preparation and extraction area will cabinet to carry out extractions not only as a contamination prevention measure but nation is unlikely to be present. The extraction area should have a biological safety shared facility (e.g. media preparation) so long as an extraneous source of contami- workflow, gowns and gloves need to be changed. preparation to extraction to amplification should be followed; if returning against the be used for all steps, including the reagent preparation. A workflow of reagent equipment (e.g. pipettes and centrifuges). Aerosol barrier tips (or equivalent) should material is disposed of correctly. Each area should have dedicated gowns, gloves and (e.g. pipettes and centrifuges). Aerosol barrier tips (or equivalent) should be used for all steps, including the reagent preparation. A workflow of reagent preparation to extraction to amplification should be followed; if returning against the workflow, gowns and gloves need to be changed. The PCR reagent preparation needs to take place in a clean room but this could be a shared facility (e.g. media preparation) so long as an extraneous source of contami- nation is unlikely to be present. The extraction area should have a biological safety cabinet to carry out extractions not only as a contamination prevention measure but also as the samples might themselves represent an exposure hazard to the worker. Aliquotting of reagents both in the PCR reagent preparation and extraction area will minimize problems should contamination be found to occur. The extracted material can be added to the PCR reagents in this room and then transferred to the thermal cycler in the amplification area. It has been recommended that for recycling of equipment (e.g. test-tube racks) and for the cleaning of workbenches that a 1:10 dilution of standard bleach be used. It is likely that cleaning with a germicidal detergent is equally effective.

2. Prevention of HCV infection

World Health Organization estimates that as many as 170 million persons worldwide might be infected with HCV. In Asia, the estimated figures range from 0.3% of the population in New Zealand to 4% in Cambodia. Data for the Pacific region are difficult to obtain, but estimates of an HCV antibody rate of up to 4.9% have been recorded in some parts of the Pacific. In the Middle East, levels of 12% have been reported in some centers. Data available on the incidence of new cases of hepatitis C are scanty because of the difficulty in differentiating between new cases and the initial diagnosis of chronically infected subjects. As the relative importance of the various modes of transmission of HCV varies from country to country, the incidence of new cases will also vary. Better data are required to confirm any changes in incidence. However, there is little doubt that the epidemiology of HCV infection in the Asia-Pacific region is chang- ing. In the new millennium, with the introduction of universal screening of blood products and the abolition of paid blood donation, injecting drug use (IDU) has become the most common route of HCV transmission.

In Australia, IDU is the admitted risk factor for chronic HCV infection in 65% of patients seen in hospital clinics. Furthermore, IDU is considered responsible for nearly all new infections. Some data indicate that the risk of transmission of HCV can be reduced by harm reduction methods (e.g. needle exchange programs and public education). However, the high prevalence of IDU in the community has meant a continuing high incidence of new HCV infections. Despite the illegal status of illicit drug injection, consideration should be given to more widespread application of harm reduction strategies.

The data concerning risk factors for transmission of hepatitis C in other regions in Asia are relatively sparse. In Japan, the lower prevalence of hepatitis C in younger compared to older people suggests that the incidence of HCV infection is decreasing. The use of traditional therapies (including acupuncture, folk remedies and Suidama) has been a major source of past transmission for HCV in some regions of Japan and Taiwan. In some countries, tattooing, including eyebrow tattooing in Vietnam and Cambodia, might be an important risk factor for transmission of the infection.

There is evidence that medical practices such as using non-disposable glass syringes and needles have been an important mode of HCV transmission. Transfusion of blood and blood products prior to HCV screening have also been a major mode of HCV transmission. However, the introduction of universal blood donor screening can virtually eliminate post-transfusion hepatitis C. The lack of universal screening of blood donors in some areas of Asia is still responsible for new cases of hepatitis C in those areas. Some contemporary medical practices still carry a risk of HCV transmission from blood contamination, particularly hemodialysis. Such transmission can be prevented with the use of universal infection control precautions.

Mother-to-baby spread has been demonstrated in approximately 7% of HCV RNA-positive mothers. Although there have been a few studies on the prevalence and risk of mother-to-infant transmission of HCV from the Asia–Pacific region, the different definition of mother-to-infant transmission used in these studies makes comparison of the data difficult. Possible criteria for more rigorous definition of mother-to-infant transmission of HCV infection include: (i) detectable anti-HCV in an infant aged older than 18 months; (ii) detection of HCV RNA in an infant aged 3–6 months of age; (iii) detection of HCV RNA in an infant on at least two occasions; (iv) elevated serum amino transaminases in an infant; or (v) identical genotype between mother and child. Co-infection with HIV and high blood levels of HCV-RNA correlate with the risk of perinatal transmission. Long-term follow-up studies have shown a low prevalence of HCV-related clinical signs and symptoms among vertically infected children in the first 10–15 years of life. Approximately 20% of children appear to clear the infection, 50% have evidence of chronic asymptomatic infection, and about 30% have evidence of chronic infection with elevated transaminase levels. Sexual transmission does occur, but is rare. There are few data regarding prevention in this situation, but concurrent sexually transmitted diseases and sexual practices that could involve blood contamination might increase the risk of HCV transmission. Common sense recommendations to reduce spread of HCV in the household setting (such as not sharing razors, avoiding blood contaminations) and by sexual transmission have been referred to in previous authori- tative documents.
2. Consensus Statements: Prevention of HCV infection

2.1. All countries must introduce universal screening of blood donors for hepatitis C antibody (anti-HCV) with third or fourth generation EIAIs. More data on the cost-effectiveness of nucleic acid testing for universal screening of blood products is required. (II-2)

2.2. In healthcare settings, adherence to universal precautions for infection control is essential. This should include use of disposable or adequately sterilized materials for invasive procedures, and adequate cleansing and sterilization of instruments. (II-2)

2.3. As transmission of HCV via IDU is an increasing trend in the Asia-Pacific region, it is important to implement an education campaign about the harm of drug use, especially among school-age children. Harm reduction programs such as needle syringe programs should also be implemented. It is important to educate tattooists and practitioners of traditional or alternative therapies about ways to minimize blood contamination. This involves sterilization techniques for procedures that involve skin penetration or breaks to mucosal surfaces. (II-2)

3. Natural history of HCV infection

The natural history of hepatitis C is quite variable. There are some inherent drawbacks in studying natural history. Firstly, it is difficult to ascertain the exact time of acquisition of infection; second, primary infection is commonly asymptomatic and thirdly disease progression is slow. Natural history data reported in the literature vary according to the type of study (retrospective vs prospective). Different study populations also result in different predictions about natural history (patients attending liver clinic vs blood donors vs community based studies vs post-transfusion cohorts). In spite of these variations there are some generalizations that can be made.

In acute HCV infection:

- 20–30% of patients are symptomatic
- Fulminant hepatic failure is very uncommon
- Elevation in serum alanine aminotransferase (ALT) levels occurs approximately 2–8 weeks after exposure
- HCV RNA can be detected in serum within 1–2 weeks after exposure
- HCV RNA levels increase progressively and peak before ALT rise and development of symptoms.
- 20–50% of patients might clear the virus spontaneously.
- Symptomatic patients and women are more likely to clear the virus.
- Most patients who clear infection do so within the first 12 weeks
- 50–80% of patients will develop chronic infection.

In chronic HCV infection:

- Up to 20–30% of patients will develop a progressive liver disease leading to cirrhosis and hepatocellular carcinoma (HCC)
- Cirrhosis rates begin to become significant after 20 years of infection
- HCC rates begin to become significant after 30 years of infection
- Factors associated with disease progression include duration of infection, age at the time of acquisition of infection, sex, alcohol consumption, immunosuppression (e.g. HIV coinfection or organ transplant recipients), obesity and insulin resistance, coinfection with other viruses, elevated aminotransferases and genetic factors
- Although elevated ALT suggests active liver damage, normal ALT does not exclude significant liver disease

- Progression to cirrhosis can be best predicted on baseline histological parameters such as the activity of necroinflammation and stage of fibrosis
- Once patients develop cirrhosis, HCC develops at approximately 1–4% per year and is increased in patients with raised α-fetoprotein levels at baseline.

3.3. In chronic HCV infection, elevated serum ALT suggests progressive liver damage. However, normal ALT does not exclude significant liver disease. A fibrosis score (Metavir score >2 or Ishak score >3) suggests progressive liver disease.

3.4. In patients with HCV related liver cirrhosis, risk of hepatic decompensation is approximately 3–4% per year; 1.4–6.9% per year for HCC. In patients with well-compensated HCV cirrhosis the 10-year survival rate is 80%. However, if there are features of decompensation, the survival rate is significantly reduced, i.e. to approximately 25%. HCC is a frequent and life-threatening complication of chronic HCV infection. In cirrhotic patients, a surveillance program for the early detection of HCC should be offered. (II-2)

4. Treatment of HCV infection

Before a discussion of specific therapies, some general points need to be made. The desired end-point of treatment of HCV infection is viral clearance, as indicated by non-detectability of HCV RNA in serum by the most sensitive test available.

- Rapid virological response (RVR) is defined as non-detectability of serum HCV RNA (<50 IU/mL) after 4 weeks of therapy.
- Early virological response (EVR) is defined as undetectable HCV RNA (<50 IU/mL) or at least a 2 log decrease in serum HCV RNA from baseline level after 12 weeks of therapy. Studies using pegylated (peg)-IFN showed that 65–72% of subjects with EVR went on to develop a SVR.
- End-of-treatment virological response (ETVR) is indicated by non-detectability of HCV RNA at the end of therapy.
- Sustained virological response is defined as undetectable serum HCV RNA (<50 IU/mL) 24 weeks after the end of therapy.
- Low viral load (LVL) is defined as serum HCV RNA < 400 000 IU/mL
- High viral load (HVL) is defined as serum HCV RNA > 400 000 IU/mL.

An SVR is the best correlate of beneficial changes in hepatic fibrosis, prevention of HCC and improvement in other clinical outcomes. SVR has been shown to have the following beneficial effects: (i) fibrotic regression; (ii) substantially reduced rate of HCC; (iii) decreased rate of other complications, including liver failure and liver-related death; and (iv) improved quality of life.
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).

With improved treatment results, the value of liver biopsy is being questioned because of the potential risks of the procedure and concerns regarding sampling error. Clinical, biochemical and imaging findings can identify many patients with advanced cirrhosis, but not those with lesser degrees of fibrosis. A liver biopsy would be useful in this latter group of patients. Although liver fibrosis markers are commercially available, they are currently insufficiently accurate to support their routine use.

Specific issues regarding therapy in acute and chronic HCV infection will now be addressed.

In acute HCV infection, serum HCV RNA is usually detected before the appearance of anti-HCV and is often the only diagnostic indicator of this condition. Acute hepatitis C infection often becomes chronic, especially in asymptomatic individuals. However, up to 50% of patients who presented with symptoms can spontaneously resolve their infection. Female sex and infection by HCV genotype non-1 increase the chance of spontaneous resolution. Spontaneous resolution is less likely after 12 weeks of infection. 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 chronic hepatitis C.

Studies using daily induction doses of conventional IFN-α, as well as those using peg-IFN-α for 24 weeks, have achieved high rates of SVR in acute hepatitis C. Peg-IFN-α has been found to be superior to conventional IFN-α plus ribavirin. Addition of ribavirin to IFN-α or peg-IFN-α has not resulted in significant improvement in SVR rates. HCV genotypes 2, 3 and 4 respond better than HCV genotype 1. It is recommended that patients infected with HCV genotype 1 be treated for 6 months. Because of small numbers of patients with HCV genotypes 4, 5 and 6 in the various studies, the most appropriate duration of therapy for persons infected with these HCV genotypes is unknown. Patients with LVL have an increased SVR. Recent data showed that patients with low levels of HCV genotype 1 who lose their serum HCV RNA after one month of therapy (rapid virological response; RVR) would need only 6 months of treatment with the standard combination therapy. However, data are conflicting on whether patients with HCV genotype 2 or 3 with LVL who achieved loss of serum HCV RNA after 1 month of treatment should be considered for 12–16 weeks of therapy. Any positive data regarding this applies more to patients with HCV genotype 2 than genotype 3.

Studies of peg IFN-α plus ribavirin have shown that 6 months’ treatment is sufficient for persons infected with HCV genotypes 2 and 3. 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. Because of small numbers of patients with HCV genotypes 4, 5 and 6 in the various studies, the most appropriate duration of therapy for persons infected with these HCV genotypes is unknown. Patients with LVL have an increased SVR. Recent data showed that patients with low levels of HCV genotype 1 who lose their serum HCV RNA after one month of therapy (rapid virological response; RVR) would need only 6 months of treatment with the standard combination therapy. However, data are conflicting on whether patients with HCV genotype 2 or 3 with LVL who achieved loss of serum HCV RNA after 1 month of treatment should be considered for 12–16 weeks of therapy. Any positive data regarding this applies more to patients with HCV genotype 2 than genotype 3. The recommended dose of peg-IFN-α2a is 180 μg weekly and the recommended dose of peg-IFN-α2b is 1.5 μg/kg bodyweight. Ribavirin doses of 1000 mg daily are recommended for persons up to 75 kg in weight and 1200 mg for persons more than 75 kg in weight.

The success rate of obtaining an SVR following HCV treatment has improved since the last APASL consensus statement in 2000. In randomized controlled trials, the highest overall SVR rates have been achieved with the combination of once a week subcutaneous injection of long acting peg-IFN-α combined with daily oral ribavirin for 1 year. This is the current standard treatment, especially for patients infected with HCV genotype 1. Peg-IFN is produced by binding polyethylene glycol to IFN molecules resulting in slower absorption from subcutaneous sites and decreased renal clearance leading to increased half-life.

There are two licensed peg-IFN-α products available for use in the Asia–Pacific region. Two large phase 3 studies using weekly doses of the two different peg-IFN-α, both combined with daily ribavirin, given for 48 weeks have demonstrated improved efficacy with higher SVR rates when compared to three times weekly standard IFN plus daily ribavirin combination. Patients infected with HCV genotypes 2 and 3 had SVR rates over 80%. A study showed that 6 months’ treatment is sufficient for persons infected with HCV genotypes 2 and 3. 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. Because of small numbers of patients with HCV genotypes 4, 5 and 6 in the various studies, the most appropriate duration of therapy for persons infected with these HCV genotypes is unknown. Patients with LVL have an increased SVR. Recent data showed that patients with low levels of HCV genotype 1 who lose their serum HCV RNA after one month of therapy (rapid virological response; RVR) would need only 6 months of treatment with the standard combination therapy. However, data are conflicting on whether patients with HCV genotype 2 or 3 with LVL who achieved loss of serum HCV RNA after 1 month of treatment should be considered for 12–16 weeks of therapy. Any positive data regarding this applies more to patients with HCV genotype 2 than genotype 3. The recommended dose of peg-IFN-α2a is 180 μg weekly and the recommended dose of peg-IFN-α2b is 1.5 μg/kg bodyweight. Ribavirin doses of 1000 mg daily are recommended for persons up to 75 kg in weight and 1200 mg for persons more than 75 kg in weight.

The relative contraindications for IFN and ribavirin (RBV). They include:

- Present or past psychosis or severe depression
- Uncontrolled seizures
- Hepatic decompensation
- Pregnancy (RBV)
- Renal failure (RBV)
- Severe heart disease (RBV).

The relative contraindications for IFN and ribavirin are:

- 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 (RBV)
- Anemia/ischemic vascular disease (RBV).

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There are few absolute contraindications for use of peg-IFN-α and ribavirin (RBV). They include:

- Present or past psychosis or severe depression
- Uncontrolled seizures
- Hepatic decompensation
- Pregnancy (RBV)
- Renal failure (RBV)
- Severe heart disease (RBV).

The relative contraindications for IFN and ribavirin are:

- 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 (RBV)
- Anemia/ischemic vascular disease (RBV).
In addition to these contraindications, special caution is required if IFN is administered in the following circumstances:

- Neutropenia (neutrophil count <1500 cells/μL³)
- Thrombocytopenia (platelet count <85 000/μL³)
- Organ transplantation
- History of autoimmune disease
- Presence of thyroid autoantibodies
- Age older than 70 years.

Testing prior to starting IFN with ribavirin treatment is indicated to identify those who might be at special risk of adverse effects, and monitoring during therapy is recommended mainly to prevent serious adverse events. The incidence and types of side-effects of peg-IFNα plus ribavirin. Side-effects related to IFN include: cytopenia, abnormalities of thyroid function, depression, irritability, concentration and memory disturbances, visual disturbances, fatigue, muscle aches, headaches, nausea and vomiting, loss of appetite and weight, low grade fever and skin irritation, insomnia, hearing loss, tinnitus, interstitial fibrosis and hair thinning. Side-effects associated with ribavirin include hemolytic anemia, fatigue, itching, rash, cough, gastrointestinal upset, pharyngitis, gout and birth defects. It is essential that persons who take ribavirin 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. The adverse events due to ribavirin and IFN can be controlled by erythropoietin and granulocyte colony stimulating factor (GCSF).

What about patients who do not achieve an SVR? This includes primary non-response and relapse. Sustained virological response can be achieved by re-treatment with peg-IFNα and ribavirin in up to 40% of subjects who failed to respond to peg-IFNα monotherapy and in 10% of subjects who failed to respond to peg-IFNα and ribavirin. Up to 50% of subjects who relapse after initial treatment with IFN monotherapy have also been found to achieve SVR after re-treatment with peg-IFN and ribavirin combination. Genotypes 2 and 3 and LVL were positive predictors in such subjects. Studies are ongoing on the effects of peg-IFN plus ribavirin combination on patients who relapse after successful treatment with standard IFN monotherapy. There is some evidence that re-treatment might have secondary benefits of reducing inflammation and fibrosis progression and possibly reversing early cirrhosis. These could translate to a delay in the development of HCC. These findings have not been tested in well-documented trials. Such trials are ongoing and no recommendation can be offered with regards to the value of maintenance therapy. Maintenance IFN or peg-IFN therapy could be considered in patients with severe fibrosis as no definitive therapy to achieve SVR is available currently.

Apart from IFN-based therapies, some comment needs to be made about the use of complimentary therapies as they are in wide use in the Asia–Pacific region.

The aims of adjuvant or complementary therapy in chronic HCV infection are:

- To improve SVR
- To decrease hepatic fibrosis, particularly in those with non-SVR
- To improve symptoms.

No proposed adjuvant or complementary therapy has been shown to improve SVR or to retard fibrotic progression. Combination therapies involving thymosin-α1 and amantadine have been considered. Therapies that have been proven to reduce serum ALT might be considered in the absence of the effective treatment to achieve SVR. Such adjuvant therapies might include phlebotomy, ursodeoxycholic acid and strong neomorphogen-C (SNMC). Phlebotomy (or other measures to reduce iron stores), o xo f n, non-steroidal anti-inflammatory drugs and amantadine (or its analogs) have been found to be not beneficial. Thymosin-α1 has shown some promise alone or in combination with IFN-α, but larger studies are required.

During use of herbal medicines alone, and especially in combination with antiviral therapy, patients should be monitored for hepatic, renal or pulmonary toxicity. In patients with a non-response to IFN or combination IFN/ribavirin therapy, vitamin E, thymosin-α1, interleukin-10, ursodeoxycholic acid, TJ-9 (Sho-saiko-to), glycyrrhizin and possibly other herbal medicines (silymarin) might be worthy of further evaluation for their effects on hepatic fibrosis and risk of HCC development.
5. Special groups

5.1. HCV infection in liver transplant candidates

The increasing global burden of the hepatitis C epidemic is now reflected by the rising prevalence of HCV-related end-stage liver disease (ESLD) and HCC. Liver transplantation is now the accepted treatment for ESLD and for small HCC arising within a cirrhotic liver. Consequently, HCV-related ESLD and HCC is now the leading indication for adult elective liver transplants performed in Europe, North America and Australasia and this proportion is likely to exceed 50% of all transplants within the next decade.

Minimal listing criteria for elective liver transplantation for HCV-related ESLD are identical to other causes of chronic liver failure. In general, transplantation should be considered in any patient with significantly shortened life expectancy or severely impaired quality of life. Survival of patients with cirrhosis can be crudely predicted by the Child–Pugh score: a score ≥10 is generally considered appropriate indication for listing. A more objective scoring system, utilizing bilirubin, INR and serum creatinine led to the development of the model for end-stage liver disease (MELD) score. This has been used to predict short-term mortality and has been adapted in North America to both reduce waiting list registrations (those with MELD <15 are unlikely to receive a graft) and waiting list mortality (as sickest patients are now prioritized).

Other than Child–Pugh score and MELD, universally accepted specific indications for listing include diuretic-resistant ascites or hepatorenal syndrome, hepatopulmonary syndrome, intractable encephalopathy and small HCC.

The Milan criteria for HCC (unresectable single HCC less than 5 cm, or up to three lesions less than 3 cm as determined by preoperative imaging) have been adopted in most transplant programs around the world. The UCSF group has reported similar results with expanded criteria (single HCC less than 6.5 cm, or up to three lesions with combined diameter of 8 cm).

All patients listed for HCC should undergo triphasic computed tomography (CT) or magnetic resonance imaging (MRI) at least 12-weekly to ensure that their tumor remains within acceptable transplant criteria.

In candidates who are serum HCV RNA positive prior to transplant, recurrent HCV infection of the allograft is universal following liver transplantation and probably occurs at the time of reperfusion. Viremia levels start to rise from day 7 and most patients will develop acute hepatitis C 4–12 weeks post-transplant, accompanied by a steep rise in HCV viral load. A small number of patients (2–5%) develop severe cholestatic hepatitis, characterized by extremely high levels of viremia, and severe cholestasis. Despite anecdotal reports of rescue with antiviral therapy and immunosuppression reduction, most progress rapidly to graft failure and death. Results of re-transplantation are extremely poor.

In most patients, graft dysfunction settles spontaneously and viremia levels plateau at 1–2 log units higher than pretransplant levels. Spontaneous clearance has not been observed. Thereafter, most patients develop chronic hepatitis C in the graft. The natural history of chronic hepatitis C is accelerated in liver transplant recipients, with 10–30% progressing to allograft cirrhosis within 5 years. The outcome following decompensation of recurrent cirrhosis is extremely poor and the results of re-transplantation are disappointing.

Graft and patient survival has improved steadily in HCV negative recipients over the last decade, thanks to advances in immunosuppression, surgical techniques, intensive care and anti-infective prophylaxis. However, the opposite has been observed in HCV positive recipients and has been attributed to changes in donor quality and immunosuppression.

The rate of HCV-induced fibrosis is accelerated in recipients who receive livers from older donors, and the average age of the deceased donor has increased from under 40 years to over 50 years since 1990.

Early reports of more severe recurrence following live-donor liver transplantation were based on biochemistry rather than histology and confounded by small numbers and limited follow-up. Larger studies containing protocol biopsies over several years have observed similar rates of fibrosis and graft survival following live-donor and deceased-donor liver transplantation.

The effects of corticosteroids on recurrent hepatitis C appear complex. In transplant recipients without HCV infection, an
episode of steroid-responsive rejection is associated with increased patient and graft survival. In contrast, steroid-responsive rejection is associated with reduced survival in recipients with HCV infection, suggesting an adverse effect of corticosteroids on the natural history of recurrent hepatitis C. High-dose intravenous steroid therapy for acute rejection leads to an early and massive increase in the hepatitis C viremia following liver transplantation and is associated with earlier onset and more rapid progression of recurrent hepatitis C. These observations suggest that steroid-sparing immunosuppressive protocols might be beneficial in patients with recurrent hepatitis C. To date, however, steroid-sparing protocols have failed to demonstrare benefit.

The worsening outcome for HCV observed over the past decade has also been linked to the popular practice of rapid tapering and early discontinuation of steroids early post-transplant. Maintaining patients on low-dose prednisone long-term might prevent rapid progression of recurrent hepatitis C.

Cyclosporine directly inhibits HCV replication in vitro through inhibition of cyclophyllin rather than calcineurin. However, this antiviral effect is weak and limited to genotype 1b. Randomized studies have not demonstrated any difference between tacrolimus and cyclosporine-treated patients in either incidence or severity of recurrent hepatitis C.

Liver transplant recipients represent a “born-to-lose” population for IFN and ribavirin. Many have already failed IFN-based therapies prior to transplant. In addition, immunosuppression is associated with HVL, reduced HCV-specific T-cell responses, and reduced first-phase viral decline following IFN, all negative baseline predictors for SVR. However, the major reason for reduced efficacy in recurrent hepatitis C following liver transplantation is the poor adherence to therapy: more than 80% of patients reduce one or both drugs, 30% withdraw completely and less than 50% achieve in 48 weeks and histological benefits are not seen. At this time, pre-emptive therapy should only be considered within the context of clinical trials.

Second, treatment can be given shortly after transplantation before the development of acute hepatitis (so called “pre-emptive” treatment). Pre-emptive treatment (to prevent recurrent hepatitis C) is complicated by poor tolerability of both IFN and ribavirin in the early post-transplant phase. Of those few patients who do qualify, results are disappointing; less than 10% achieve SVR after 48 weeks and histological benefits are not seen. At this time, pre-emptive therapy should only be considered within the context of clinical trials.

Third, treatment can be considered after chronic hepatitis (usually >6 months) has been established in the allograft. When patients with chronic recurrent hepatitis C are treated with 48 weeks of peg-IFN plus ribavirin, SVR is achieved in 20–40% and is associated with histological improvement. Best cure rates are achieved in patients infected with HCV genotype 2 and 3 (60–70%). Currently, combination peg-IFN plus ribavirin should be considered in any patient with significant (≥ stage 2) fibrosis or with early cholestatic hepatitis C.

In patients with HCV undergoing liver transplantation, antiviral therapy can be considered in three clinical situations. First, treatment may be considered while awaiting transplant. In patients with advanced liver disease, IFN therapy might produce immune-mediated hepatitis flares associated with decompensation and death. In a pilot study of 32 patients with Child B or C cirrhosis (mean Child–Pugh score = 12 ± 1),128 less than half were suitable for IFN treatment. Of the 15 who were treated, only 33% had ETVR and none achieved SVR, 85% had serious adverse events and one patient died, forcing early closure of recruitment. In a second study of patients listed for transplant but with less advanced disease (mean Child–Pugh score = 7 ± 2), a low accelerating dose regimen was better tolerated, with serious adverse events in 19% and no deaths. Thirty patients achieved SVR (24%), of whom half were delisted for improvement. Twelve patients were transplanted after successful SVR, none of whom have subsequently relapsed. Results from these and subsequent studies would support antiviral therapy for those patients with Child–Pugh score ≤7, MELD score ≤18, platelet count >60 000, thus limiting its use in the pretransplant setting to those patients with well compensated disease, either listed for HCC or awaiting live-donor liver transplantation.

5.1. Consensus Statements: HCV infection and liver transplantation

5.1.1. Patients with a decompensated hepatitis C can be considered for antiviral treatment, provided they have Child–Pugh score ≤7 and MELD score ≤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, infections and correct cytopenias are recommended. (II-2)

5.1.2. In patients with hepatitis C being considered for liver transplantation, minimal listing criteria should be identical to those for other primary liver diseases. (II-2)

5.1.3. Following liver transplantation, pre-emptive treatment post-transplant to prevent recurrent hepatitis C (>6 months post-transplant) should only be within clinical trials. (II-2)

5.1.4. Treatment of established recurrence (>6 months post-transplant) should be considered in those with severe disease. The preferred regime is at least 48 weeks peg-IFN plus ribavirin. (I)

5.1.5. Over-immunosuppression should be avoided in the early post-transplant period. (II-2)

5.1.6. Rapid steroid withdrawal should also be avoided in the later post-transplant period. (III)
5.2. HCV infection in end-stage renal disease\textsuperscript{148-170}

HCV-associated renal disease might occur in about 10% of patients with chronic HCV infection. There are three principal types of renal diseases that have been recognized: mixed cryoglobulinemia, membranoproliferative glomerulonephritis and membranous nephropathy. These disorders can occur both in native kidneys and in renal allografts. There is increased prevalence in African-Americans, Asian men and patients with HVL. All patients with mixed cryoglobulinemia, membranoproliferative glomerulonephritis and membranous nephropathy should be evaluated for possible underlying HCV infection. Most HCV infected patients with nephropathy will have evidence of liver disease as reflected by elevated serum aminotransferase concentrations. However, serum aminotransferases are normal in some cases and a history of acute hepatitis is often absent. Combined IFN-\(\alpha\) and ribavirin is still the mainstay of treatment; however, ribavirin dosage needs adjustment if the creatinine clearance is less than 50 mL/minute. Peg-IFN plus ribavirin can be used in most patients with HCV-induced renal disease in view of the convenience and improved rate of SVR with this regime in patients with chronic HCV infection. However, this recommendation can only be applied to patients with normal or near-normal renal function.

Once patients are on dialysis support therapies, particularly hemodialysis, they are at risk of acquiring HCV infection. Since the introduction of crythropoietin and screening of blood products for anti-HCV, the risk of acquiring post-transfusion HCV infection has declined to less than 1 per 3000 units of blood products transfused. However, HCV infection still does occur. The duration of dialysis is a risk factor in acquiring HCV infection. Among units with an anti-HCV prevalence of <19%, the annual incidence of anti-HCV seroconversion is 2.5%. By comparison, in units with a prevalence of >60% the annual incidence of seroconversion is 35.3%. The data suggest that the hemodialysis machines themselves do not have a significant role in the nosocomial transmission of HCV. It is likely that HCV transmission in hemodialysis settings principally results from a breakdown of universal infection control guidelines resulting in horizontal (patient-to-patient or staff-to-patient) transmission.

The safety of peg-IFN in moderately advanced renal failure is yet to be confirmed. Concerns largely revolve around its long half-life. Likewise ribavirin and its metabolites are not removed by dialysis therapies. Thus ribavirin therapy in patients with advanced renal failure results in profound and prolonged hemolytic anemia. Until data that demonstrate efficacy and safety are available, peg-IFN or ribavirin cannot be recommended in patients with end-stage renal disease unless they are enrolled in a clinical trial.

There are, however, data on the use of standard IFN monotherapy. Two meta-analyses have been performed showing that IFN therapy alone is associated with an SVR of 32–36%. In five of the studies, the standard regime of subcutaneous IFN administration 3 million units three times weekly for 24 weeks was associated with an SVR of nearly 40%. In addition, IFN-\(\alpha\) therapy is advisable for HCV infected dialysis patients who are candidates for renal transplantation. A regime of 3 million units three times weekly for 12 months appears to be safe and effective in inducing biochemical and virological responses.

Liver disease following renal transplantation occurs among 19–64% of recipients with HCV infection compared to only 1–30% among recipients without HCV infection. An unusual form of liver disease with severe cholestasis and rapidly progressive liver failure has been described in a few patients with HCV infection who undergo renal transplantation. To better assess the effects of HCV infection on outcome of post-transplantation, a meta-analysis was performed of eight observational studies that included 6365 patients. The presence of anti-HCV antibodies increased the relative risk for death by 1.79 (95% confidence interval 1.7–2.3). A major stumbling block to the use of IFN-\(\alpha\) in renal transplant recipients has been the onset of acute rejection with IFN treatment. Thus post-transplant IFN is not recommended because of serious risks of rejection and allograft loss.

5.3. HCV infection in thalassemia and hemophilia\textsuperscript{171-193}

Blood transfusion has historically been one of the main sources of HCV transmission globally, and still remains so in many parts of the world where blood is not adequately screened. It is therefore no surprise that patients with transfusion-dependant blood disorders are at high risk of acquiring HCV infection. Moreover, with improved management of chronic blood disorders, concurrent problems such as chronic HCV infection can now cause greater morbidity and mortality in these patients than the original disease.

Worldwide, the carriers of hemoglobinopathies are estimated to total 269 million and most of them live in the Asia. \(\beta\)-Thalassemia has a gene frequency of >1% in India, South-East Asia and parts of Far East Asia, which means that nearly 80 000 infants with hemoglobinopathies are born each year in the region. The prevalence of HCV infection in patients with thalassemia in Asia is high and varies from 20% in Thailand to 64% in Iran. Patients are generally infected with HCV during the first 10 years of life and persistence of HCV infection is favored by iron overload and various immune abnormalities underlying susceptibility to infections.

HCV infection and iron overload might act as synergistic risk factors for the development of liver cirrhosis and HCC. In patients with thalassemia who were followed up after bone marrow transplantation with serial liver biopsies, 22% showed progressive fibrosis with mean time to progression of 51 months. The prob-
ability of fibrosis progression-free survival was significantly lower in patients who were HCV positive and had high liver iron content. More significantly, the development of HCC in patients with chronic HCV infection might occur at a much earlier age in those with thalassemia compared to those without. Clearly the treatment of chronic HCV in these patients has become imperative, along with the management of iron overload.

The standard treatment of chronic HCV infection is the combination of IFN and ribavirin. However, according to earlier guidelines, the use of ribavirin has been thought to be contraindicated in thalassemic patients because hemolysis is a side-effect. Thus there has been concern that combination therapy would result in a further increase in liver iron burden and exacerbate liver damage. Earlier treatment series have therefore reported the use of IFN monotherapy. These have generally been small non-randomized studies that have used standard IFN 3 million units three times weekly for 6–18 months. In general, the SVR has been higher the longer the duration of therapy (45% with 12 months and up to 77% with 18 months of therapy).

More recently, there have been case series of combination therapy and one randomized trial comparing monotherapy with peg-IFN to combination therapy with ribavirin. The combination arm showed a somewhat better SVR but there was an increase in blood transfusion requirements in the combination therapy group, with a transfusion required every 3–4 weeks to maintain hemoglobin of 9–10 mg/dL.

As iron overload is an independent predictor of progression of liver fibrosis in patients with thalassemia, it is also imperative that adequate and vigorous iron chelation therapy is provided. However, whether iron depletion improves the response of HCV infection to IFN therapy is still a matter of debate, with a number of randomized trials showing no improvement of SVR with iron depletion in those without thalassemia.

Finally, with the advent of bone marrow transplantation for the treatment of thalassemia, it has become opportune to consider the optimal timing for HCV treatment. In general, these patients are able to discontinue immunosuppression 1 year after receiving a bone marrow transplant. Treatment for HCV should be considered only after patients have been off all immunosuppression therapy for 6 months and when there is no evidence of graft versus host disease or myelosuppression.

Due to the frequent requirements of pooled plasma and blood transfusions, patients with hemophilia remain at a high risk of blood borne viral infections, particularly in developing areas of the world where screening of blood and blood products might not be adequate. The prevalence of HCV in patients with hemophilia has been reported to be as high as 70–95%. It seems that the natural history of HCV in children is that of a very slowly progressive, but probably irregular fibrotic process. Cirrhosis, liver failure and liver transplantation have been reported in childhood, but these events are rare.

The diagnosis of perinatally acquired HCV requires a positive anti-HCV test after 18 months of age. HCV PCR might not detect HCV infection at birth. However, the specificity of HCV PCR is 98% from birth and hence the positive predictive value of PCR is high. As in adults, HCV PCR might be intermittently negative. Although there is no evidence that antiviral treatment is detrimental in children, it is not generally available. However, children might be offered antiviral treatment in countries wherever this is available on a compassionate use basis. Small studies using a combination of peg-IFN-α2a or 2b together with ribavirine have shown excellent SVR of 100% in genotype 2 and 3 and approximately 45% in genotype 1. As it is not possible to predict which children will develop significant fibrosis or cirrhosis during childhood, all children with HCV should be reviewed every 6 to 12 months.

### 5.3. Consensus Statements: HCV infection in thalassemia and hemophilia

5.3.1. Patients with thalassemia or hemophilia who have chronic HCV infection should be considered for antiviral treatment. (1)

5.3.2. In patients with thalassemia it is uncertain whether peg-IFN monotherapy or combination therapy with ribavirin is the best option. (II-2)

5.3.3. Following bone marrow transplantation, treatment for HCV in thalassemia should be considered after immunosuppression therapy has been stopped. (II-2)

5.3.4. The value of a liver biopsy in patients with hemophilia is uncertain. If considered necessary, liver biopsy should only be performed by experienced operators. (II-2)

### 5.4. HCV infection in children

The prevalence of HCV infection in children is low (<3%) in several large studies from the Asia–Pacific region. Most new HCV infections in children are perinatally acquired with a risk of around 5%. This risk is increased if the mother has HIV; however, neither elective caesarean section nor breast feeding increase the rate of transmission. The majority of children with HCV infection are clinically well with normal or mildly elevated transaminases. The natural history of HCV in children is that of a very slowly progressive, but probably irregular fibrotic process. Cirrhosis, liver failure and liver transplantation have been reported in childhood, but these events are rare.

The diagnosis of perinatally acquired HCV requires a positive anti-HCV test after 18 months of age. HCV PCR might not detect HCV infection at birth. However, the specificity of HCV PCR is 98% from birth and hence the positive predictive value of PCR is high. As in adults, HCV PCR might be intermittently negative. Although there is no evidence that antiviral treatment is detrimental in children, it is not generally available. However, children might be offered antiviral treatment in countries wherever this is available on a compassionate use basis. Small studies using a combination of peg-IFN-α2a or 2b together with ribavirine have shown excellent SVR of 100% in genotype 2 and 3 and approximately 45% in genotype 1. As it is not possible to predict which children will develop significant fibrosis or cirrhosis during childhood, all children with HCV should be reviewed every 6 to 12 months.
5.5. HCV and HIV coinfection

The prevalence of HIV among HCV-positive patients varies according to distribution of HCV risk categories and presence of HIV prevention strategies. Highest HIV/HCV coinfection prevalence is seen in settings where IDU is the major HCV risk factor and harm reduction strategies such as needle and syringe programs are unavailable. Hepatitis C has a limited impact on HIV disease progression. Conversely HIV alters the natural history of hepatitis C in several important areas: (i) progression to chronic hepatitis C is increased; (ii) levels of HCV viral load are higher; (iii) rates of progression to cirrhosis and ESLD are increased two- and six-fold, respectively; (iv) HCC occurs at a younger age; and (v) the risk of antiretroviral related hepatotoxicity is increased up to threefold in HIV/HCV coinfected patients (the risk is particularly high in those receiving nevirapine containing regimes).

Liver disease is an increasing component of HIV-related morbidity and mortality. Maintenance or restoration of immune function through highly active antiretroviral therapy (HAART) reduces the impact of HIV on hepatitis C natural history, in particular progression to cirrhosis and ESLD. SVR rates following peg-IFN and ribavirin therapy in HIV/HCV coinfected patients are 15–20% lower than in HCV monoinfection, but predictors of treatment response are largely hepatitis C factors: genotype, HCV viral load, and liver disease stage. Rates of hepatic decompensation in HIV/HCV coinfected patients during hepatitis C treatment are considerably higher than in HCV monoinfected patients, with patients with cirrhosis at particularly high risk.

5.5.1. Routine screening is recommended for HIV in patients with hepatitis C following exposure risk assessment and pretest counseling.

5.5.2. HIV/HCV coinfected patients with advanced HIV disease (CD4 count <100/mm³) should receive HAART with HCV treatment delayed until immune function is improved, preferably to a CD4 count above 200/mm³. (I)

5.5.3. Antiretroviral therapy naïve HIV/HCV coinfected patients with a CD4 count 100–350/mm³ should commence HAART prior to HCV treatment. (I)

5.5.4. HIV/HCV coinfected patients with a CD4 count >350/mm³ should be considered for HCV treatment and do not require HAART. (I)

5.5.5. Peg-IFN 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)

5.5.6. Deferral of HCV treatment should be considered in HIV/HCV coinfected patients with HCV genotype 1 and HVL (>800 000 IU/mL) if early liver disease (F0/1) is demonstrated on liver biopsy. (I)

5.5.7. There is insufficient evidence to support HCV treatment of patients with persistently normal ALT levels, but treatment could be considered in those with moderate or severe fibrosis. (II-2)

5.5.8. Didanosine should be avoided during HCV treatment due to the increased risk of hyperlactemia and hepatic decompensation. (II-1)

5.6. HCV and HBV coinfection

It is not clear how many patients are coinfected with HCV and HBV worldwide; however, the prevalence of dual infection with both viruses seems low among a randomly selected healthy population. It is reported that among anti-HCV positive patients, at least 2% are also positive for hepatitis B surface antigen (HBsAg), whereas in HBsAg positive patients the prevalence of anti-HCV is 3–20% in the Asia–Pacific region. Coinfection with both viruses is thought to be associated with mutual inhibition of viral replication. It is well described that HCV infection suppresses HBV replication both in vitro and in vivo. The overall dominant effect appears to be HCV suppression of HBV. However, liver disease is worsened in coinfection. In general fibrotic disease progression in dually infected patients is faster than that in mono-infected patients. The progression to cirrhosis and decompensated liver disease is accelerated and the relative risk of developing HCC is also increased.

5.6.1. It is recommended to routinely screen for HBsAg in patients with chronic HCV infection, especially in IDU or other high risk populations.

5.6.2. It is not justified to recommend routine measurement of serum HBV DNA in HBsAg negative patients with chronic HCV infection.

5.6.3. HCC screening tests including liver ultrasound and α-fetoprotein should be done for coinfected patients.

5.6.4. HBV and HCV coinfected patients may be selected for antiviral treatment by the same criteria as those with monoinfection.

5.6.5. It is helpful to determine which virus is dominant in patients with dual infection before treatment.

5.6.6. In patients who are anti-HCV and HBsAg positive and HCV PCR positive, peg-IFN-α combined with ribavirin is recommended.

5.6.7. For patients who are anti-HCV and HBsAg positive but HCV PCR negative with detectable serum HBV DNA at significant levels, peg-IFN-α or nucleos(t)ide analogs or both can be used.

5.6.8. HBV vaccination should be offered for hepatitis C patients who are HBsAg negative.

5.7. HCV infection and extrahepatic manifestations

It is recognized that some patients with chronic HCV infection might suffer from extrahepatic illnesses with the spectrum varying from fatigue to permanent organ damage. HCV can replicate in mononuclear cells and other tissues but to determine replication itself might be problematic and requires special techniques such as detection of negative-strand HCV RNA or strand specific RT-PCR through the use of recombinant Tth enzyme. Extrahepatic diseases in HCV infection are thought to be mediated with by immune complexes (e.g. mixed cryoglobulinemia, glomerulonephritis, cutaneous vasculitis and neuropathy) or by direct immune stimulation. (e.g. lymphoproliferative disorders
and non-Hodgkin’s lymphoma (NHL)). Some symptoms, such as depression, fatigue and porphyria cutanea tarda (PCT), occur by undefined mechanisms.

In mixed cryoglobulinemia, immunoglobulin complexes formed by HCV RNA and rheumatoid factor precipitate in the walls of small and medium blood vessels and produce lesions similar to leukocytoclastic vasculitis. The prevalence of cryoglobulinemia in chronic HCV infection is 40–44% but only about 10% of cryoglobulinemia is symptomatic. Many studies have revealed the pathogenic importance of HCV itself in these illnesses by showing resolution following an SVR as a result of antiviral treatment.

In some patients, HCV-associated vasculitis might be life-threatening due to severe peripheral vascular disease, gastrointestinal ischemia and central nervous system involvement. In such situations the use of anti-CD20 monoclonal antibody (rituximab) therapy with or without plasmapheresis has been effective.

HCV-associated neuropathy seems to result from immune complex deposition within the vasa nervorum of the peripheral nerves. This might affect up to 50% of patients with chronic HCV infection. Patients usually present with painful symmetrical distal polyneuropathy, which can be progressive. The illness might respond well following plasmapheresis or antiviral therapy.

Low grade B-cell NHL with predominantly extranodal tissue involvement, such as liver, spleen, salivary glands and stomach, is reported to be more common in patients with chronic HCV infection. HCV might trigger B-cell proliferation and cause high-grade lymphoma. Although there are no definite treatment options, remission has been described after HCV eradication in some subsets of splenic and gastric mucosa-associated lymphoid tissue (MALT) lymphoma. Screening for HCV infection in all patients with splenic lymphomas and other types of low grade B-cell NHL is strongly recommended.

Nearly 50% of patients with PCT have chronic HCV infection. The prevalence is reported to be as high as 60% in southern Europe and Japan. The mechanism of PCT in this setting is unclear. It has been postulated that an imbalance of oxidative stress within hepatocytes and interference of uroporphyrin metabolism might be responsible. The treatment includes cessation of precipitation factors (alcohol, hormone, immune) followed by antiviral treatment.

Some studies have revealed associations between urticaria, cutaneous polyarthritis nodosa and cutaneous lichen planus in chronic HCV infection but with no proven mechanisms. Arthralgia and myalgia has been reported to be found in 20% of patients with chronic HCV infection. Arthritis is usually characterized by symmetrical small joint involvement.

Fatigue might be the most common extrahepatic manifestation of chronic HCV infection, with up to an 80% prevalence. Risk factors include female sex, age >50 years and cirrhosis but there is no correlation with viral load and genotype. Improvement of fatigue and quality of life are usually found in patients with SVR.

The basis for depression and other psychological symptoms in HCV infection has been difficult to determine but it remains intriguing that some investigators have found evidence of HCV infection in the central nervous system with the characterization of quasispecies that differ from liver and peripheral blood compartments.

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