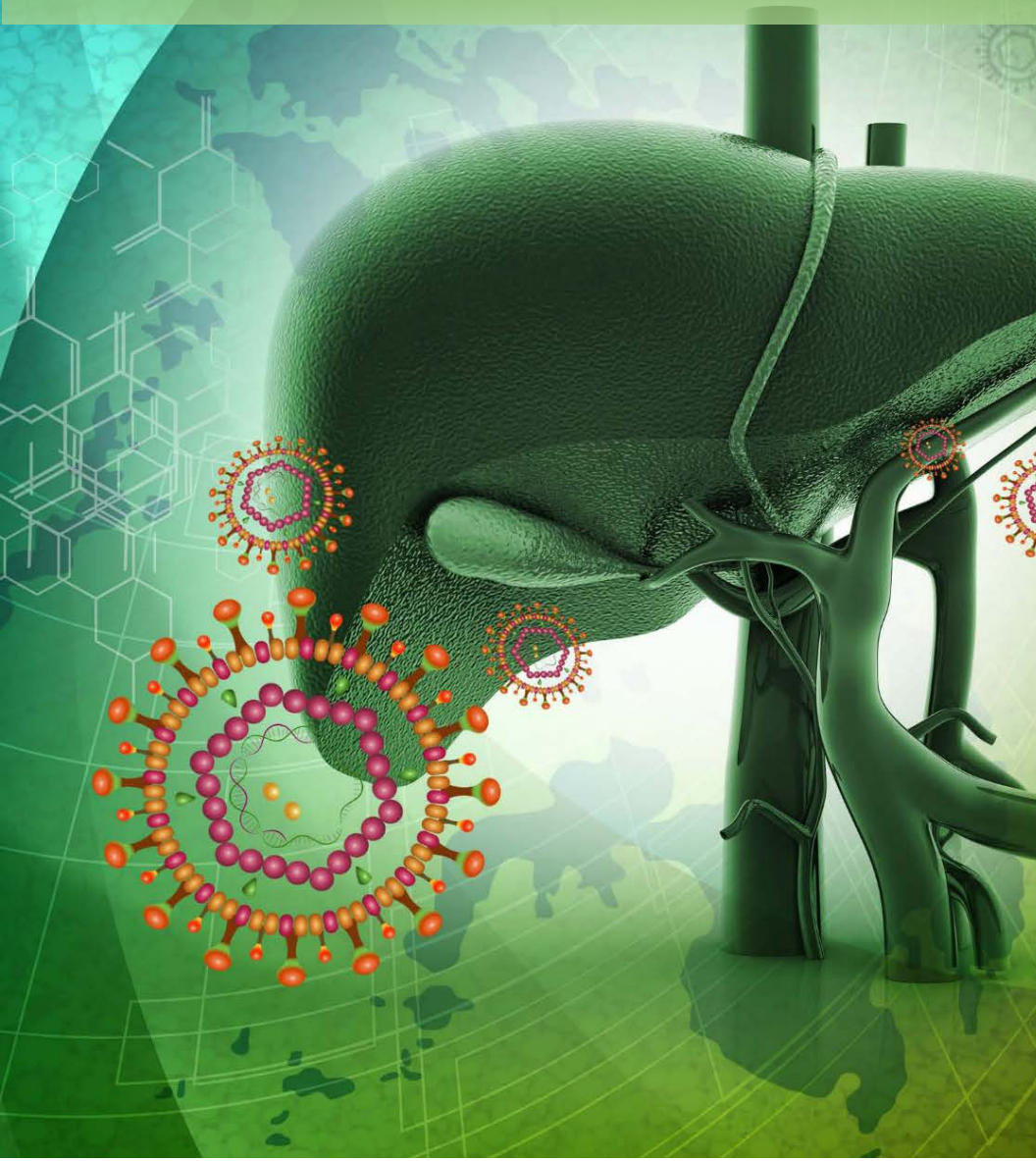
2006 Hepatology Society of the Philippines

The 2014 Hepatology Society of the Philippines Consensus Statements on the Diagnosis and Treatment of Hepatitis C



The 2014 Hepatology Society of the Philippines Consensus Statements on the Diagnosis and Treatment of Hepatitis C

Hepatology Society of the Philippines (HSP) **Hepatitis C Virus Consensus Core group:**

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Foreword:

Hepatitis C virus (HCV) infection is a devastating disease that is increasingly being diagnosed among Filipinos, especially in at-risk populations. There are disease-specific nuances in the evaluation and management of this infection. Furthermore, advances in the field brought about by clinical research are rapidly moulding the way we evaluate and manage HCV patients. Evidently, consensus statements formulated by experts in the field are needed in order to serve as a guide to physicians who see these patients in the clinic. With this in mind, the Hepatology Society of the Philippines spearheaded the formation of these statements which aimed to address issues in the diagnosis, evaluation, treatment, and follow-up care of patients with HCV infection. Recommendations on the specific tests to perform in the evaluation of HCV patients before, during and after treatment, and first-line treatment of patients with acute and chronic HCV infection were provided. Treatment algorithms for chronic HCV infection, divided according to viral genotype, were also devised. We acknowlege the limitations brought about by the local inavailability of some drugs/treatment regimens in the local setting at the time of the formulation of these statements. As such, these statements will be revised as soon as new data become locally applicable.

Introduction:

Hepatitis C infection is an emerging public health problem in the Philippines and exacts a huge economic and social burden among infected patients. Small-scale studies suggest that up to 1% of Filipinos could be infected with the hepatitis C virus (HCV).[1] Chronic HCV infection may cause liver cirrhosis and hepatocellular carcinoma (HCC) after several years.[2] Worldwide, hepatitis C is responsible for 27% of cirrhosis, and 25% of HCC cases.[3] HCC carries a poor prognosis and is the second leading cause of cancer death locally.[4,5]

As a roadmap for a comprehensive and multisectoral action to control viral hepatitis, the National Viral Hepatitis Task Force, a private-public partnership convened by the Hepatology Society of the Philippines, published a position paper titled *Prevention and Control of Hepatitis B and Hepatitis C in the Philippines: A Call to Action*.[6] The paper highlighted the need to improve the quality of care received by hepatitis C patients. A crucial step in achieving this goal is the development of national consensus statements that will provide guidance to clinicians managing these patients. We acknowledge that the treatment of HCV is a fast-growing and evolving area of medical research. Therefore, these statements will be amended as new data and treatments become available.

Methodology:

The development of the current consensus statements on the management of HCV infection was spearheaded by the Hepatology Society of the Philippines. Initially, a Knowledge, Attitudes and Practices (KAP) survey on the diagnosis and management of HCV infections was conducted to determine major gaps and deviations in clinical practice. Based on the results of this survey, the following clinical questions were developed:

- How to diagnose and who to screen for hepatitis C?
- Who are the candidates for treatment?
- What work-ups are necessary prior to and during treatment?
- What is the available standard-of-care treatment?
- What are the stopping rules and modification rules (response-guided therapy or RGT) during treatment?

A core group of ten members were selected to review the current evidence. The members were chosen for their expertise, academic affiliations, active clinical practice and research in hepatitis C. Literature searches were performed in Medline, Embase, and the Cochrane Central Register of Controlled Trials. Manual searches in bibliographies of key articles including those published in the Philippine Journal of Internal Medicine (PJIM) and Philippine Journal of Gastroenterology were likewise done. Local data gathering was also performed through a review of scientific papers submitted by fellows-in-training from different accredited training institutions of the Philippine Society of Gastroenterology (PSG). The GRADE system was used to appraise the quality of available evidence and define the strength of recommendation (Table 1).[7] After data review, 24 statements were proposed following the modified Delphi process. A recommendation was rated as “strong” if the effects of an intervention clearly outweigh the undesirable effects (or conversely, clearly do not), as a result of the quality of evidence, presumed patient-important outcomes, and cost. A recommendation was considered “discretionary” if trade-offs are less certain either because of low quality of evidence, or desirable and undesirable effects are closely balanced, or there is higher cost or resource consumption.

The statements were then presented in a hepatitis C consensus conference to a panel representing various stakeholders for voting. Each panel member was allowed to vote one of the following for each statement: A) accept completely; B) accept with some reservation; C) accept with major reservation; D) reject with reservation; and, E) reject completely.

Table 1. GRADE quality of evidence[7]

Quality	Definition
High quality	Further research is very unlikely to change our confidence in the estimate of effect
Moderate quality	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low quality	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very low quality	Any estimate of effect is very uncertain

A statement was accepted if the combined votes for choices A and B reached 80% of the voting panel, and rejected if they did not reach 80% or if at least one member voted D or E. If a statement was rejected, core group members and panel members proposed revisions to the statement, and the revised statements were again put to a vote. This was repeated until a consensus statement was accepted or completely rejected.

The definitions of commonly used terms in this manuscript are enumerated in Table 2.

Table 2. Definition of terms

Rapid virologic response (RVR)	Undetectable hepatitis C virus (HCV) RNA at week 4 of therapy using real-time polymerase chain reaction (PCR) assay in patients treated with pegylated interferon (peg-IFN) and ribavirin combination
Partial early virologic response (pEVR)	More than 2 $\log_{10}$ decrease in HCV RNA from baseline but still detectable at week 12 of therapy in patients treated with peg-IFN and ribavirin combination
Complete early virologic response (cEVR)	HCV RNA detectable at week 4, but undetectable at week 12 of therapy in patients treated with peg-IFN and ribavirin combination
End-of-treatment response (ETR)	Undetectable HCV RNA at the end of therapy
Sustained virologic response (SVR)	Undetectable HCV RNA 24 weeks after the end of therapy
Null response	Less than 2 $\log_{10}$ decrease in HCV RNA from baseline at week 12 of therapy in patients treated with peg-IFN and ribavirin combination
Partial response	More than 2 $\log_{10}$ decrease in HCV RNA from baseline at week 12 but still detectable at week 24 of therapy in patients treated with PEG-IFN and ribavirin combination
Relapse	Reappearance of HCV RNA any time after the end of therapy in patients with ETR

Consensus Statements:

Screening and Diagnosis

Statement 1. Screening with serum anti-HCV should be done for patients at risk of acquiring the disease. (High quality, Strong) Testing for anti-HCV should not be routinely performed as a prerequisite for employment. (Moderate quality, Strong)

HCV is transmitted via the following routes: infected blood and body fluids (i.e., transfusion of infected blood and blood products, sharing of contaminated personal items such as razors and toothbrushes, unsanitary body modification including unregulated tattooing or body piercing, reuse of contaminated medical equipment, and needle sharing in people who inject drugs), sexual transmission, and vertical transmission from mother to infant.[8-16]

Table 3 summarizes the characteristics of patients that are at risk of infection. Persons who received blood products prior to 1995 should be tested for HCV because of Republic Act 7719, also known as the National Blood Services Act, which was enacted in 1994 and mandated testing of all donated blood products for transmissible diseases including HCV. However, this was fully implemented only the year after and documented only in some institutions.[17] Therefore, it is important for clinicians to confirm when the Act was fully implemented in their respective localities. Body piercings performed in hospitals or clinics are considered safe. Unsafe body piercing may include acupuncture in some instances, depending on precautionary measures conducted in the facility. Unsafe sexual practices may include non-use of effective barrier contraception (i.e., condoms), males having sex with males, and having multiple sexual partners.

Table 3. Persons at risk for acquiring hepatitis C virus (HCV) infection

History of transfusion of blood and/or blood products , and organ transplantation prior to 1995 (High quality, Strong)
End stage renal disease patient on maintenance hemodialysis (Low quality, Strong)
History of intranasal use or injection of illicit drugs (Moderate quality, Strong)
History of acquiring a tattoo and body piercing in an uncontrolled environment (Low quality, Strong)
Incarceration (Low quality, Discretionary)
Unprotected sex with an HCV-infected partner (Low quality, Discretionary)
Unsafe sexual practices (High quality, Strong)
Being born to an HCV-infected mother (Low quality, Discretionary)
Close household contacts of HCV-infected patients (Low quality, Strong)
Persistently elevated levels of alanine aminotransferase (Low quality, Strong)
History of needle-stick and other sharps injury, or mucosal exposure (Low quality, Discretionary)

Family members of HCV-infected patients should be tested at least once for anti-HCV. After a history of needle-stick and other sharps injury, or mucosal exposure, testing for HCV ribonucleic acid (RNA) may be performed within 4 weeks, and anti-HCV may be performed after 12 to 24 weeks.

Since patients with HCV infection and compensated liver disease can be asymptomatic, have no functional impairment, and cannot transmit the infection through casual contact in the workplace, HCV is not a contraindication for gainful employment.

Statement 2. Screening for anti-HCV antibodies should be done using third- or fourth-generation enzyme immunoassay or chemiluminescent immunoassay. (High quality, Strong)

There are a number of diagnostic tests for hepatitis C. Screening for HCV should ideally be done using a sensitive diagnostic test for the presence of serum anti-HCV. Third-generation tests displayed a sensitivity of 98.9% (95% CI: 94-100%) in patients with chronic liver disease, and 97.2% (95% CI: 92-99%) in panels of sera.[18] Fourth-generation combination antigen-antibody assays, where two markers of the same infection could be detected simultaneously, appeared more suitable in a blood bank setting where large numbers of donor samples need to be screened in the shortest possible time.[19] The combined antigen-antibody assays are usually sandwich enzyme lined immunosorbent assays (ELISA) where the solid phase and second phase comprise both HCV derived antigens and antibodies against HCV.

Statement 3. Quantification of serum HCV RNA should be made by a sensitive assay (ideally a real-time polymerase chain reaction (PCR) assay with a lower limit of detection of less than 10-15 IU/mL) and expressed in IU/ml. HCV RNA quantification should be done in the following circumstances:

- **Patients who tested positive for serum anti-HCV (High quality, Strong)**
- **Patients being considered for anti-viral treatment (High quality, Strong)**
- **Patients suspected to have acute HCV infection (High quality, Strong), patients who are immunocompromised and suspected to have exposure to HCV, even if anti-HCV is negative (Moderate quality, Strong)**

A sensitive quantitative HCV RNA assay is not only useful to confirm the diagnosis of HCV infection in patients with positive serum anti-HCV, but also quantifies viral load, which is helpful in treatment planning and monitoring during treatment. In addition, anti-HCV may be negative and HCV RNA could be the only marker of infection during the first 2 to 8 weeks of acute exposure and in immunocompromised patients who are unable to mount an antibody response. Therefore, patients suspected to have HCV infection, including acute HCV infection, as well as immunocompromised patients who are suspected to have had HCV exposure, should undergo quantification of serum HCV RNA.[20] Based on this recommendation, the clinician should identify immunocompromised patients (i.e. human immunodeficiency virus [HIV]-infected patients, end-stage renal disease patients, and etc.). Patients who will receive treatment for HCV should also undergo baseline HCV RNA quantification to adequately monitor treatment response.

Statement 4. Patients with positive serum anti-HCV but negative HCV RNA should be re-tested for HCV RNA after 4-6 months. (Strong, Moderate quality)

Patients with positive serum anti-HCV but with a negative test for HCV RNA may represent acute HCV infection during a period of transient clearance of HCV RNA, a false positive anti-HCV result, or resolution of HCV infection.[21] Re-testing for HCV RNA is recommended 4 to 6 months later to confirm the resolution of HCV.[20]

Statement 5. Acute HCV infection should be suspected in patients with any of the following:

- **Seroconversion from negative to positive anti-HCV status within 24 weeks (High quality, Strong)**
- **Clinical symptoms (including jaundice) or severe elevation of alanine aminotransferase (ALT) more than 10 times the upper limit of normal (ULN) in a patient with seropositivity for anti-HCV and/or HCV RNA. Other causes of severe hepatitis should be excluded (High quality, Strong)**

Acute hepatitis C is defined as the presence of HCV infection for less than 24 weeks. Documentation of seronegativity for anti-HCV 24 weeks prior to an initial finding of positive serum anti-HCV is a strong indication of acute HCV infection. Although majority of patients with acute HCV infection are asymptomatic,[22,23] patients who do develop symptoms usually manifest signs and symptoms consistent with acute viral hepatitis (e.g., fever, headache, malaise, anorexia, nausea, vomiting, diarrhea, and abdominal pain), or develop jaundice with or without markedly elevated serum ALT levels.[24] The latter represents a patient subset that has to be differentiated from patients with decompensated liver cirrhosis, since these patients may also present with non-specific constitutional symptoms and jaundice. However, patients with liver cirrhosis will usually have physical stigmata of cirrhosis, laboratory results suggestive of cirrhosis such as thrombocytopenia and hypoalbuminemia, and rarely present with ALT > 10 times the ULN. Other causes of acute hepatitis such as viral hepatitis A, B, C and E, autoimmune hepatitis, drug-induced liver injury, Wilson's disease, and ischemic hepatitis have to be excluded in patients with markedly elevated ALT levels. The presence of acute HCV infection is confirmed in suspected patients by the documentation of detectable HCV RNA in the serum.

Statement 6. Chronic hepatitis C should be proven by the presence of both anti-HCV antibodies and HCV RNA. (High quality, Strong)

Chronic hepatitis C is certain in a patient with chronic liver disease when both anti-HCV and HCV RNA are detected using a sensitive technique.[21] Detection of chronic HCV infection is often predicated on an initial positive anti-HCV testing, after which HCV RNA should be tested. Detectable serum HCV RNA confirms the presence of chronic HCV infection, whereas undetectable serum HCV RNA warrants repeat HCV RNA testing after 4 to 6 months to exclude the rare possibility of intermittent negative viremia.[25] For patients who have a high index of suspicion for HCV infection but with a high likelihood of false negative anti-HCV result (e.g., immunocompromised patients), HCV RNA testing and anti-HCV testing should be done at the same time. If HCV RNA is detected, the diagnosis of HCV infection is confirmed.

Statement 7. Patients with acute or chronic HCV infection should be counseled for appropriate monitoring and to prevent disease transmission. (High quality, Strong)

Since patients with acute or chronic HCV infection can transmit the infection to others, they should be counseled on behaviors that minimize the risk of transmission.[20] HCV-infected persons should be counseled to avoid sharing toothbrushes and dental or shaving equipment.[24] They should be instructed to cover any bleeding wounds to minimize contact of their blood with others. Intravenous drug users should be counseled to stop illicit drugs. Those who continue to inject drugs should avoid needle sharing and reuse. They should be advised to clean the injection site with a new alcohol swab, and to dispose of paraphernalia in a safe, puncture-proof container. They should be advised to not donate blood, body organs, other tissue or semen.

The risk of transmission is low in a monogamous relationship, and infection itself is not a reason to change sexual practices in this situation.[24] However, those in other high risk relationships should be encouraged to practice safe sex (e.g., use of barrier precautions).

In addition, patient should be counseled on minimizing harm and maximizing treatment outcomes. Avoidance of alcohol should be encouraged.[20,26] Compliance to treatment aimed at attaining sustained viral response (SVR) should also be emphasized.

Statement 8. Vaccination against hepatitis A and hepatitis B should be given to HCV-infected patients who test negative for anti-HAV IgG, and HBsAg and anti-HBs, respectively. (High quality, Strong)

Co-infection with other hepatitis viruses may increase morbidity in HCV-infected patients. Among patients with chronic hepatitis C, higher rates of serious complications such as fulminant hepatitis were reported during co-infection with hepatitis A.[26] Likewise, chronic hepatitis C patients also had more severe hepatitis and higher risk of cirrhosis in the setting of hepatitis B superinfection.[27,28] It is thus prudent to prevent co-infection through vaccination of patients who do not have preexisting antibodies to hepatitis A and B.

Baseline and On-treatment Assessment

Statement 9. The decision to treat a patient with chronic hepatitis C should take into account the following factors: (High quality, Strong)

- **Liver disease severity**
- **Risk of side effects from treatment**
- **Likelihood of treatment response**
- **Co-morbid conditions**
- **Patient's readiness to undergo treatment and availability of socio-economic support**
- **In the absence of contraindications, treatment should be strongly considered in patients who meet treatment criteria. (Table 4)**

Untreated patients with chronic hepatitis C can progress to liver cirrhosis and development of HCC.[2] In contrast, patients who respond to treatment achieve histologic improvement, and have lower risk of liver decompensation and reduced liver-related morbidity and mortality.[29-38] Therefore, unless contraindications are present or the current severity of liver disease precludes drug administration, treatment should be strongly considered.[39,40] The contraindications for combined pegylated interferon (peg-IFN) and ribavirin therapy are hypersensitivity to IFN alpha, ribavirin, *Escherichia coli-derived* products, polyethylene glycol or to any component of the drug preparation, and pregnancy. Patients with decompensated cirrhosis and neonates and infants up to 3 years old are not candidates for peg-IFN containing treatment.[39] Patients with concomitant autoimmune hepatitis may experience a flare in their autoimmune disease when exposed to peg-IFN and can only be started on IFN-containing therapy when the underlying autoimmune disease is suppressed with immunosuppressive therapy. Furthermore, when boceprevir is added to the combination, additional contraindications include hypersensitivity to boceprevir and any of its components; co-administration with medicines that are highly dependent on cytochrome P3A4/5 for clearance, and for which elevated plasma concentrations are associated with serious and/or life-threatening events such as orally administered midazolam and triazolam, bepridil, pimozide, lumefantrine, halofantrine, tyrosine kinase inhibitors, simvastatin, lovastatin, quetiapine, alfuzosin, silodosin, and ergot derivatives (dihydroergotamine, ergonovine, ergotamine, methylergonovine); and pregnancy.[40]

The ability to adhere to treatment and tolerate adverse drug reactions should also be considered.[20,36,37] Patients who fulfilled the 80/80/80 rule (received more than 80% of peg-IFN, more than 80% of ribavirin, and were treated for more than 80% of the planned duration of treatment) had a 63% SVR rate compared with 52% in those with less than 80% adherence.[41] This effect was found to be particularly important for HCV genotype 1 patients, highlighting the importance to reduce side effects and motivate patients to adhere to treatment, especially in difficult to treat genotype 1 patients. Other factors that may affect adherence or tolerability include co-morbid conditions and patient-related factors such as willingness to treat and the availability of psychosocial support, which is important for any form of chronic medical treatment.

Table 4. Patient characteristics that determine suitability for treatment (Strong, Moderate quality)

Patient characteristics where treatment is widely accepted	Patient characteristics where treatment is not recommended
• Age 18 years or older • Serum HCV RNA positive • Significant fibrosis on liver biopsy or transient elastography • Compensated liver disease (total serum bilirubin <1.5 g/dL; INR <1.5; serum albumin >3.4 g/L, platelet count >75,000/mm^3 and no evidence of hepatic decompensation (hepatic encephalopathy or ascites) • Acceptable hematological and biochemical indices (hemoglobin >13 g/dL for men and >12 g/dL for women; neutrophil count >1,500/mm^3; and serum creatinine <1.5 mg/dL • Willing to be treated and to adhere to treatment requirements • Normal ALT to $\leq$10 x ULN. Higher ALT levels may be considered if hepatic decompensation is not a concern	• Major uncontrolled depressive illness • Decompensated liver disease • Solid organ transplant recipient • Autoimmune hepatitis or other autoimmune condition known to be exacerbated by pegylated interferon • Untreated thyroid disease • Pregnant or unwilling to comply with adequate contraception • Severe concurrent medical disease such as severe hypertension, heart failure, significant coronary heart disease, poorly controlled diabetes, chronic obstructive pulmonary disease • Age less than or equal to 3 years • Known hypersensitivity to drugs used to treat HCV

HCV=hepatitis C virus; RNA=ribonucleic acid; INR=international normalized ratio; ALT=alanine aminotransferase; ULN=upper limit of normal.

The clinician should also evaluate the patient's baseline likelihood of treatment response. There are many viral and host factors affecting treatment response, and not achieving an SVR might be related to a combination of any of these factors. HCV genotype and interleukin 28B (IL28B) host genotype are the strongest predictors of peg-IFN/ribavirin therapy outcome.[42-44] Other factors predicting poor treatment response include high viral load, older age, black race, and advanced fibrosis or cirrhosis.[42-47]

Patients with normal or near-normal ALT should also be considered for treatment. While HCV-infected patients with persistently normal ALT have been excluded from registration trials, it has been shown that combination peg-IFN and ribavirin treatment in these patients had similar SVR rates as those with elevated ALT levels.[48]

Statement 10. At baseline and before treatment with combination therapy, the following should be performed: (High quality, Strong)

- **Medical history and clinical examination**
- **Baseline laboratory: liver biochemistry (ALT and aspartate aminotransferase or AST), liver synthetic function (albumin, prothrombin time and bilirubin), renal function (creatinine), thyroid function (TSH, T4) and complete blood count (CBC)**
- **Quantitative serum HCV RNA with a PCR-based assay**
- **HCV genotyping**
- **Liver biopsy or noninvasive methods of determining liver fibrosis**
- **Cardiac and pulmonary evaluation, if clinically indicated**
- **Psychiatric evaluation, if clinically indicated**
- **Pregnancy test when applicable**
- **Serum HBsAg in all patients and HIV-ELISA in those with risk factors for HIV**

A thorough baseline or pre-treatment asessment is necessary to assess liver disease severity, to determine likelihood of treatment response, to identify those at risk for treatment-related side effects, to search for co-morbidities, and to search for other concurrent causes of liver disease. An assessment of liver fibrosis should be performed at baseline either by a liver biopsy or a noninvasive method such as transient elastography because the degree of fibrosis impacts on SVR.[38] If treatment is initiated when patients have minimal or no fibrosis (F0, F1 or F2), there is a greater probability of achieving an SVR compared to patients with advanced fibrosis (F3 or F4) (42% vs. 21%).[49] Therefore, to increase the likelihood of SVR, treatment should commence prior to the development of significant fibrosis.

Although a liver biopsy is still regarded as the gold standard to assess the grade of inflammation and stage of fibrosis, it is not mandatory to perform a biopsy before initiating treatment. A liver biopsy may be considered when information regarding stage of fibrosis and prognosis will affect the decision regarding initiating treatment.[20]

Clinical adverse events associated with IFN-alfa and ribavirin are common. Majority experience at least 1 adverse event during therapy and accounts for 10% to 14% of treatment discontinuations. Adverse events are a major reason patients do not want to be treated. Most are related to flu-like and psychiatric symptoms.

Testing for HBV and HIV (in those with risk factors) is important in HCV-infected individuals because of shared risk factors. In addition, co-infection is associated with decreased response rates and leads to more severe liver disease and increases the risk of cirrhosis and decompensation.[50,51]

Statement 11. During treatment, the following should be performed: (High quality, Strong)

- **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 initially, then every 4 weeks thereafter**
- **Serum HCV RNA at specific time points to determine the likelihood of response to or futility of treatment (table 3)**
- **Thyroid function every 3-6 months**
- **Psychiatric evaluation, if warranted**
- **Chest x-ray, ophthalmic or audiogram examination, if warranted**
- **Reinforcement of advice regarding need for effective birth control, extending up to 24 weeks after the last dose of ribavirin**

Patients should be monitored during therapy to assess response to treatment and to monitor for the occurrence of side effects. Monitoring of treatment efficacy is largely based on HCV RNA determination at specific time points (Table 5) because the likelihood of SVR is proportional to the time of HCV-RNA disappearance.[26] These time points are also useful in response-guided therapy (RGT) which allows treatment duration to be tailored based on early on-treatment response. For HCV RNA quantification, it is preferred that the same laboratory be used to monitor treatment efficacy to ensure consistency of results in each patient.

Table 5. Recommended time points for HCV RNA determination during and after treatment

Timing of HCV RNA*	**Implications in genotype 2 and 3 patients**	**Implications in genotype 1 patients**
4 weeks Used to determine RVR with peg-IFN and ribavirin combination	RVR results in a higher likelihood of SVR	Peg-IFN and ribavirin combination: Patients with RVR and baseline HCV RNA <400,000 IU/mL may shorten treatment duration to 24 weeks
8 weeks	Not applicable	Triple therapy (boceprevir + peg-IFN + ribavirin) Treatment may be shortened to 28 weeks if HCV RNA is undetectable at 8 and 24 weeks
12 weeks Used to determine cEVR, pEVR and null response to peg-IFN and ribavirin combination	Treatment discontinued if at least pEVR is not achieved	Peg-IFN and ribavirin combination: Treatment discontinued if at least pEVR is not achieved Triple therapy (boceprevir + peg-IFN + ribavirin) Treatment should be discontinued if HCV RNA is ≥ 100 IU/ml
24 weeks	Undetectable means ETR with peg-IFN and ribavirin combination	Triple therapy (boceprevir + peg-IFN + ribavirin) Treatment may be shortened to 28 weeks if HCV RNA is undetectable at 8 & 24 weeks Treatment should be discontinued if HCV RNA is still detectable
48 weeks	Undetectable means SVR with peg-IFN and ribavirin combination	For patients treated for 48 weeks, undetectable means ETR in patients with standard duration of therapy
72 weeks	Not applicable	Undetectable means SVR in patients with standard duration of therapy

*HCV RNA should be below the lower limit of detection (LLOD) of 10 to 15 IU/mL if used as criteria for shortening therapy. HCV RNA below the lower limit of quantification (LLOQ) of 25 IU/mL may be used for assessing ETR and SVR.
HCV=hepatitis C virus; RVR=rapid virologic response; peg-IFN=pegylated interferon; SVR=sustained virologic response; cEVR=complete early virologic response; pEVR=partial early virologic response; ETR=end of treatment response.

Monitoring for side effects is recommended at every visit because it can potentially affect treatment efficacy if dose modification or treatment discontinuation occurs as a result of side effects. Laboratory abnormalities are the most common reasons for dose reductions. Neutropenia occurs in approximately 1 in 5 patients treated for HCV. Severe neutropenia and serious infections are uncommon and the administration of granulocyte colony-stimulating factor is seldom necessary. Anemia occurs in approximately one third of patients within the first 6 to 8 weeks after starting therapy and stabilize

thereafter. Severe anemia (hemoglobin level of less than 10 g/dL) needing dose adjustment occurs in 9% to 15% of treated patients.[36,38,52]

Flu-like symptoms are frequent and increase in severity particularly during the first month of treatment and gradually decreases.[53,54] In contrast, fatigue, anxiety, and depression progressively increase in incidence and severity after the first month. Periodic monitoring for signs of depression and other psychological symptoms should be done because they are common during HCV therapy and impacts on treatment adherence and patient well-being. Patients should be encouraged to report symptoms of depression and consultation with a psychiatrist recommended for individuals with a history of depression and symptoms of untreated psychiatric illness on initial assessment.

Treatment may be associated with either hypothyroidism or hyperthyroidism.[55] Peg-IFN treatment may be continued with the onset of hypothyroidism, with the addition of thyroid hormone replacement. Hyperthyroidism as a result of autoimmune thyroiditis may be treated with beta-blockers with no need for carbimazole. For patients with Grave's disease and detectable thyroid stimulating antibodies and complete suppression of thyroid stimulating hormone, discontinuation of peg-IFN treatment is recommended. A referral to an endocrinologist for appropriate treatment and follow-up should be considered.

Statement 12. Surveillance for HCC is recommended in patients with liver cirrhosis by performing liver ultrasound and alfa-fetoprotein (AFP) determination every 6 months. (High quality, Strong)

Hepatitis C is identified as the fourth leading cause of HCC worldwide.[3] Risk is higher in the presence of cirrhosis, and surveillance therefore is recommended for these patients. Hepatobiliary ultrasound alone has a sensitivity of 94% to 95% in detecting subclinical HCC, but may have a significantly lower sensitivity for detecting early HCC, which is frequently smaller and harder to visualize on ultrasound.[56] In addition, infiltrating tumor morphology will interfere with the sensitivity of ultrasound, and other supporting modalities are needed. Alfa fetoprotein (AFP) has an acceptable specificity but poor sensitivity for early HCC, with only 10% to 20% of early cancers having elevated AFP. However, up to 27% of patients with HCC can have a "normal" ultrasound but still have an elevated AFP on screening.[57] This emphasizes the need for combining multiple available screening modalities in order to increase the ability to detect HCC at an earlier stage. A systematic review of mixed-etiology cohorts concluded that the most effective strategy is to screen each patient with AFP and ultrasound every 6 months.[58]

The role of surveillance in HCV-infected patients with bridging fibrosis but no cirrhosis is unclear. The point at which the risk of HCC starts to increase has not yet been defined, and transition from bridging fibrosis to cirrhosis cannot always be accurately determined.[59] The European Association for the Study of Liver Disease Single Topic Conference suggested that screening should be offered to HCV-infected patients with Metavir stage-3 fibrosis, although the cost-efficacy of this recommendation has not been fully assessed.[59,60]

Treatment of HCV infection

Statement 13. Peg-IFN alfa monotherapy should be used for treating patients with acute hepatitis C, and continued for 24 weeks in genotype 1 patients, and for 12 weeks in genotypes 2, 3 and 4 patients. (Moderate quality, Strong)

A randomized controlled trial on 131 acute hepatitis C patients, 102 of whom were randomly assigned to peg-IFN alfa-2b (1.5 mcg/kg) for 8, 12, or 24 weeks, found that SVR was best achieved after a treatment of at least 8 weeks in genotypes 2, 3, and 4; whereas genotype 1 required 24 weeks of therapy.[61] Treatment for 8 and 12 weeks was associated with fewer adverse events compared with the 24-week regimen.

However, treatment of acute hepatitis C should be delayed for 8 to 12 weeks because 21-52% of patients may have spontaneous resolution of their infection with the disappearance of serum HCV RNA. Majority of cases with spontaneous resolution occur within 12 weeks of acute HCV infection.[61-66] Conversely, commencement of therapy beyond 12 weeks of the diagnosis of acute HCV infection is not recommended because SVR will be markedly reduced as shown by Kamal et al, where SVR progressively decreased from 92% to 76% for patients treated within 12 and 20 weeks, respectively, of acute HCV diagnosis.[62] An additional finding in that trial was that unlike genotypes 2 to 4 where 12 weeks was the ideal waiting period before starting treatment, patients with genotype 1 infection were found to benefit from earlier treatment commencement (8 weeks). This highlights the need for earlier determination of HCV RNA levels, and consequently, HCV genotype, in patients with suspected acute HCV infection.

Statement 14. In genotype 1 chronic hepatitis C patients, the combination of once a week subcutaneous injection of peg-IFN alfa (2a 180 mcg; 2b 1.5 mcg/kg) combined with daily oral ribavirin (1,000 mg for patients with body weight of at most 75 kg; 1,200 mg for those weighing more than 75 kg) for 48 weeks is the standard of care (Figure 1). (High quality, Strong)

Several small-scale local studies found that genotype 1 is the most prevalent HCV genotype in the Philippines, accounting for over half of the cases.[67-70] A randomized controlled trial on 1,121 patients with chronic HCV infection genotype 1 demonstrated that a 48-week regimen of 180 mcg of peg-IFN alfa-2a once weekly plus daily ribavirin (1,000 or 1,200 mg, depending on body weight) resulted in a higher SVR rate (56%) than weekly peg-IFN alfa-2a plus placebo (44%, $p<0.001$), or 3 million units of IFN alfa-2b thrice weekly plus daily ribavirin for 48 weeks (29%, $p<0.001$).[44]

Likewise, a randomized controlled trial on 1,530 patients with chronic hepatitis C genotype 1 showed that a 48-week regimen of peg-IFN alfa-2b 1.5 mcg/kg each week plus 800 mg/day ribavirin resulted in a higher SVR rate (42%) compared to those who received peg-IFN alfa-2b 1.5 mcg/kg per week for 4 weeks then 0.5 mcg/kg per week plus ribavirin 1,000 to 1,200 mg/day (34%, $p=0.01$), or IFN alfa-2b (3 MU subcutaneously three times per week) plus ribavirin 1,000 to 1,200 mg/day orally (33%, $p=0.01$).[43]

The Individualized Dosing Efficacy vs. Flat Dosing to Assess Optimal Pegylated Interferon Therapy (IDEAL) study showed that in patients infected with HCV genotype 1, the rates of SVR and tolerability did not differ significantly between peg-IFN alfa-2a and alfa-2b containing regimens.[56] A 48-week regimen using peg-IFN alfa-2a or alfa-2b was consistently found more effective than shorter 24-week regimens.[38,71]

A trial on 235 patients with chronic genotype 1 hepatitis C with low viremia ($\leq$600,000 IU/mL) treated with peg-IFN alfa-2b 1.5 mcg/kg subcutaneously once weekly plus ribavirin 800 to 1,400 mg/day based on body weight revealed that among patients who achieved RVR at week 4, similar SVR rates were achieved in patients treated for 24 and 48 weeks (89% vs 85%; $p>0.05$).[73]

Statement 15. In genotype 1 patients with baseline HCV RNA <400,000 IU/mL and who achieves a rapid virological response (RVR) with peg-IFN alfa and ribavirin, reduction of treatment duration to 24 weeks can be considered. (High quality, Discretionary)

Patients with chronic genotype 1 infections achieve RVR 24% of the time.[72] Of these patients, SVR was achieved in 89%, higher than the SVR of genotype 1 patients in the registration trials. Those with low viral load are more likely to achieve RVR and SVR. The odds ratio (OR) of achieving RVR was 9.7 (95% CI 4.2-22.5; $p<0.0001$) for patients with baseline HCV RNA of less than 200,000 IU/mL, and 5.6 (95% CI 1.5-9.1; $p=0.0057$) for those with viral load of 200,000 to 600,000 IU/mL. Furthermore,

achieving an RVR and a baseline HCV RNA of less than 200,000 IU/mL were significant and independent predictors of SVR in patients treated for 24 weeks, with an OR of 23.7 (CI 9.1-61.7) and 2.7 (95% CI 1.1-6.3; p<0.026), respectively. It is because of the identification of these predictors of response that trials have looked at shortening treatment duration in patients with favorable baseline HCV RNA levels and RVR.

Furthermore, a meta-analysis on seven randomized controlled trials comparing shorter therapy duration vs. 48 weeks treatment with peg-IFN alfa and ribavirin among 807 HCV genotype 1 patients with RVR demonstrated that while SVR was significantly lower in patients treated for a shorter duration than with 48 weeks of therapy in the overall population, SVR after a 24-week regimen was similar to the standard 48-week regimen among patients with baseline HCV-RNA level of 400,000 IU/mL or less (mean difference: -3.10%, 95% CI -8.6% to 2.4%, p=NS).[74] The authors concluded that a 24-week combination therapy should be considered only in patients with low baseline viral load and who achieved RVR.

Statement 16. In genotype 1 patients who do not achieve undetectable HCV RNA at week 12, but achieve a $\geq$2 $\log_{10}$ decrease in HCV RNA at week 12 and undetectable HCV RNA at week 24 with peg-IFN alfa and ribavirin, prolongation of treatment duration to 72 weeks can be considered. (Moderate quality, Discretionary)

In some patients with HCV genotype 1 infection, response to peg-IFN and ribavirin combination is slow, with HCV RNA still detectable after 12 weeks despite a decrease in HCV RNA of at least a two-fold $\log_{10}$ scale (partial early virologic response). In these patients, if the HCV RNA becomes undetectable at 24 weeks, higher SVR may be achieved by extending treatment to 72 weeks instead of the standard 48 weeks. A meta-analysis on such patients with slow response to peg-IFN-alfa-2a/b plus ribavirin who received extended treatment up to 72 weeks (n=669) showed that extended treatment increased overall SVR by 14.7% (95% CI 4%-25.5%; p=0.0072).[75] The difference in SVR is mainly due to the decreased rates of viral relapse in patients who extended treatment, although end-of-treatment response rates were similar. However, it should be noted that the frequency of voluntary treatment discontinuation was significantly increased by extended therapy (7% vs 2.3%, p<0.001), although serious adverse events were not increased (8% vs 7%, p=0.25). Poor tolerance to treatment and the added expense may discourage patients from extending treatment duration.

Patients with poor predictors of SVR such as obesity, diabetes, or cirrhosis may not achieve similar outcomes for SVR, and so the complicating condition should be controlled or reversed, where applicable, before initiating therapy.

Statement 17. The addition of boceprevir to the standard treatment regimen should be considered in the following genotype 1 patients: (Moderate quality, Discretionary)

- **IL28B CT and TT genotype**
- **Treatment-naïve patients who do not have an RVR at treatment week 4**
- **Patients who relapsed after or were non-responders to peg-IFN and ribavirin therapy**
- **Patients with compensated cirrhosis**

Genotype 1 patients with a high likelihood of not responding to the conventional peg-IFN/ribavirin dual combination, such as those with IL28B CT and TT genotypes, those who fail to reach RVR at week 4, relapsers or non-responders to peg-IFN/ribavirin, and those with compensated cirrhosis, should be identified for possible addition of boceprevir into the conventional regimen.[42-47,76]

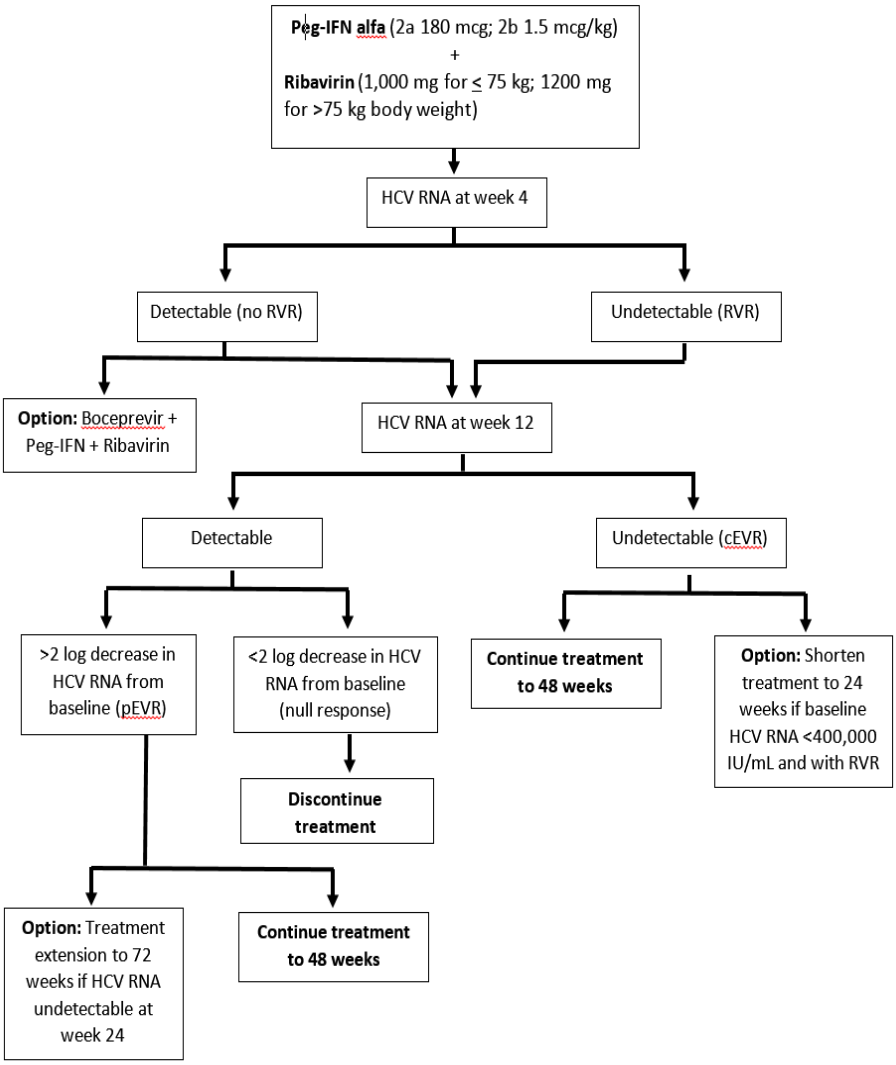
The Serine Protease Inhibitor Therapy 2 (SPRINT-2) study was a double-blind study on treatment-naïve patients with HCV genotype 1 infection treated with one of three possible regimens after a 4-week lead-in period of peg-IFN/ribavirin: placebo plus peg-IFN/ribavirin for 44 weeks; RGT with boceprevir plus peg-IFN/ribavirin; and boceprevir plus peg-IFN/ribavirin for 44 weeks.[76] Those who received peg-IFN/ribavirin only had significantly lower SVR rate (40%) compared to those in the 44 weeks triple therapy (68%; $p<0.001$) and RGT groups (67%; $p<0.001$). However, this difference in SVR between the boceprevir-containing groups and the conventional treatment (68% vs. 36%; $p<0.001$) was only reflected in the non-black cohort who did not achieve RVR after the 4-week lead-in period. It is important to note that the addition of boceprevir did not confer an advantage in SVR rate among patients who achieved RVR ($p=0.55$).

The SPRINT-2 trial also showed that boceprevir therapy was associated with higher SVR in IL28b non-CC genotype patients, increasing SVR to 68% (vs. 28% peg-IFN/ribavirin only) in CT genotype patients and 57% (vs. 27% peg-IFN/ribavirin only) in TT genotype patients. The same conclusion is true in patients who were partial responders/relapsers to previous peg-IFN/ribavirin treatment, where the addition of boceprevir led to an increase in SVR rates from 17% to 67% in CT genotype and from 50% to 66% in TT genotype patients.[76]

Retreatment of patients who were relapsers/partial responders to previous peg-IFN/ribavirin treatment with peg-IFN/ribavirin combination has consistently yielded disappointing SVR rates (16% to 18%).[77,78] Retreatment with the same regimen among these patients is not expected to improve the SVR. The addition of boceprevir into the regimen significantly increased the SVR in these patients. In the Retreatment with HCV Serine Protease Inhibitor Boceprevir and Pegintron/Rebetol 2 (RESPOND-2) trial, patients who were relapsers/partial responders to previous peg-IFN/ribavirin therapy were randomized into 3 groups: Peg-IFN/ribavirin for 48 weeks; RGT with boceprevir and peg-IFN/ribavirin; and boceprevir and peg-IFN/ribavirin for 44 weeks.[79] The boceprevir-containing arms were initially treated with a 4-week lead-in period of peg-IFN/ribavirin. The highest SVR was seen in patients treated with boceprevir plus peg-IFN/ribavirin for 44 weeks (66%) and those treated with boceprevir RGT (59%), which were significantly higher than those treated with peg-IFN/ribavirin only (21%; $p<0.001$).

Lastly, a pooled analysis of boceprevir trials demonstrated the benefit of boceprevir in HCV genotype 1 patients with liver cirrhosis (Metavir F4).[80] Patients included in the analysis of two randomized controlled studies included previously untreated (SPRINT-2) and previous treatment relapsers/partial responders (RESPOND-2). Combining the results from both studies, it was found that patients with liver cirrhosis were less likely to achieve SVR with peg-IFN/ribavirin therapy (27%) compared to the boceprevir containing regimens (49%).

Figure 1. Treatment algorithm for treatment-naïve HCV genotype 1 patients



Statement 18. The recommended dose of boceprevir is 800 mg three times per day combined with pegylated interferon alfa and weight-based ribavirin for 44 weeks, preceded by 4 weeks of lead-in treatment with peg-IFN and ribavirin alone. (Moderate quality, Strong)

- **In treatment-naïve patients with no cirrhosis, treatment duration may be shortened to 28 weeks (4 weeks lead-in with pegylated interferon alfa and ribavirin followed by 24 weeks of triple therapy) if HCV RNA at weeks 8 and 24 are undetectable**
- **In patients with cirrhosis and in prior non-responders (null and partial responders) to peg-IFN alfa and ribavirin, treatment duration should be 48 weeks (4 weeks lead-in with pegylated interferon alfa and ribavirin followed by 44 weeks of triple therapy)**
- **In previous relapsers to peg-IFN alfa and ribavirin, treatment duration may be shortened to 36 weeks (4 weeks lead-in with pegylated interferon alfa and ribavirin followed by 32 weeks of triple therapy) if HCV RNA is undetectable at weeks 8 and 12**

The recommended dose of boceprevir is 800 mg administered orally three times daily with food (administration without food could be associated with a net loss of efficacy due to sub-optimal exposure).[40,76,79] It should be administered in combination with peg-IFN and ribavirin, after a 4-week lead-in period of peg-IFN and ribavirin. The presence of an RGT boceprevir arm in both the SPRINT-2 and RESPOND-2 trials, which investigated treatment-naive patients and partial responders/relapsers to previous combination peg-IFN and ribavirin, respectively, allowed the investigation of a strategy where the duration of treatment was adjusted according to virologic responses during pre-determined periods on-treatment.[76,79]

In treatment-naive patients, RGT allowed for the shortening of triple therapy with boceprevir to 24 weeks (28 total treatment weeks, including the 4-week lead-in treatment with peg-IFN/ribavirin) if HCV RNA became undetectable at treatment week 8 and 24, while patients with detectable HCV RNA on week 8 but undetectable on week 24 continued triple therapy with boceprevir until week 28 before continuing on with dual therapy with peg-IFN and ribavirin for another 20 weeks.[40] The variable dosing with RGT resulted in an SVR rate (67%) that was equal to 44 weeks of triple therapy with boceprevir (68%) and is thus an option in treatment-naive patients without cirrhosis.

In the RESPOND-2 trial, RGT allowed for triple therapy with boceprevir to be shortened to 36 weeks (including the 4-week lead-in period with peg-IFN/ribavirin) if HCV RNA was undetectable at weeks 8 and 12.[79] If HCV RNA was detectable at week 8 but undetectable at week 12, peg-IFN/ribavirin dual therapy was continued for an additional 12 weeks beyond week 36 of boceprevir-containing triple therapy. The SVR rates of the RGT regimen versus 48 weeks of boceprevir-containing triple therapy (including the 4-week lead-in period with peg-IFN/ribavirin) was lower in the subgroup of patients who were previous partial responders (40% vs. 52%). In comparison, patients who were previous relapsers had similar SVR rates with RGT compared to the 48-week regimen (69% vs. 75%).

Patients who had a null response to previous peg-IFN/ribavirin treatment almost never achieve SVR when retreated with the same regimen.[81] Retreatment of these hard-to-treat patients with boceprevir-containing triple therapy for 48 weeks markedly increased the SVR to 38%.[82] Therefore, treatment-experienced patients who previously relapsed after peg-IFN/ribavirin therapy have an option for shortened boceprevir-containing triple therapy using RGT while partial and null responders should be treated for 48 weeks.

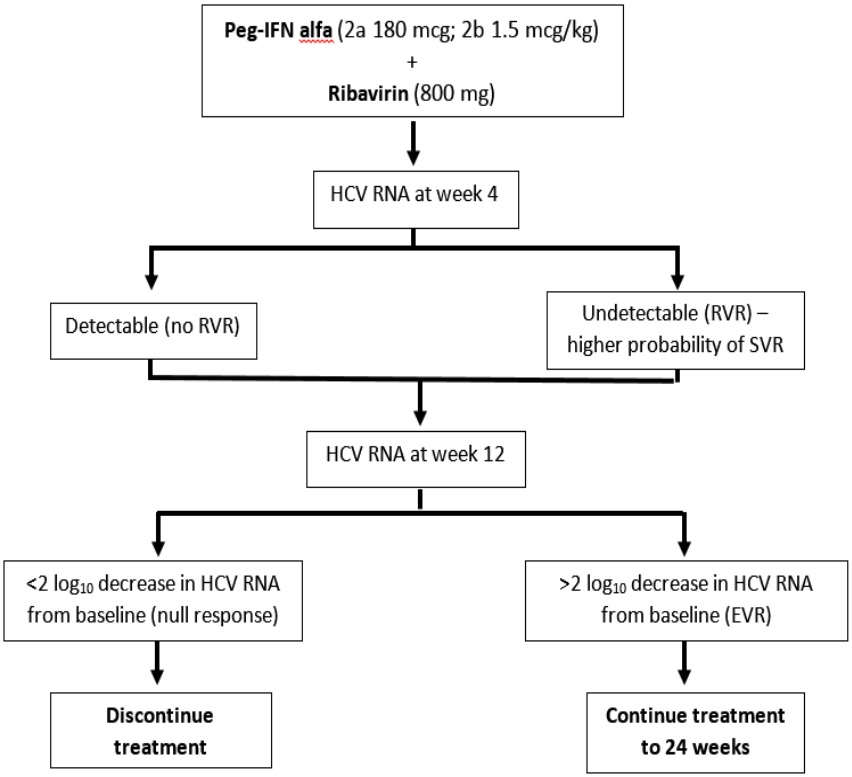
For patients with compensated cirrhosis, pooled analysis of the SPRINT-2 and RESPOND-2 trials showed that patients who received boceprevir for 44 weeks after a 4-week lead-in with peg-IFN/ribavirin achieved a higher SVR (60%) compared to those

who received peg-IFN/ribavirin only (27%) and those who received boceprevir RGT (32%).[80]

Statement 19. In genotype 2 or 3 patients, the combination of once a week subcutaneous injection of peg-IFN alfa (2a 180 mcg; 2b 1.5 mcg/kg) combined with daily oral ribavirin (800 mg) for 24 weeks is the standard of care (Figure 2). (Moderate quality, Strong)

Small-scale local studies found that HCV genotypes 2 and 3 comprise around 24% to 34% of patients with chronic HCV infection.[67] In these patients, a 24-week regimen of weekly peg-IFN plus ribavirin leads to a 75% to 80% SVR in Asians, and a 84% to 96% SVR rate in Caucasians.[38,83-86] The Study of Peginterferon Alfa-2a in Combination with Ribavirin in Interferon-Naïve Patients With Chronic Hepatitis C Infection (ACCELERATE) showed that the SVR rate from a 24-week regimen was significantly higher than that from a 16-week treatment (70% vs 62%, p<0.001).[87] The rate of relapse was also lower with the 24-week regimen (18% vs 31%, p<0.001). Patients with RVR had a SVR rate of 85% with the 24-week regimen vs 79% in the 16-week group (p=0.02).

Figure 2. Treatment algorithm for treatment-naïve HCV genotype 2 and 3 patients



Statement 20. The goal of antiviral therapy should be SVR, defined as undetectable HCV RNA by PCR assay 24 weeks after the end of therapy. (High quality, Strong)

The ultimate goal of hepatitis C antiviral treatment is to prevent progression to cirrhosis, end-stage liver disease, HCC, and death. However, a surrogate outcome is needed to guide clinicians and patients in decision making during the early stages of the clinical course, including decisions regarding antiviral treatment. SVR as defined above has been associated with clinical, laboratory, and histological improvements in chronic HCV patients. Those who achieved SVR had a lower likelihood of complications, conversion to HCC, and death; had improved liver function parameters; and had better fibrosis scores and a lower risk of cirrhosis.[34,88-91] Furthermore, SVR from IFN-based therapies for chronic HCV is usually durable, and the correlated benefits were observed for the long term.[92] Therefore, SVR should be used as a reasonable goal of antiviral treatments for HCV infections.

Statement 21. Maintenance therapy with peg-IFN alfa is not recommended to chronic HCV infected patients who do not respond to standard of care. (High quality, Strong)

Given that progression of fibrosis to cirrhosis is a function of hepatic inflammation, it has been suggested that IFN-based maintenance therapy might slow disease progression. The Hepatitis C Antiviral Long-term Treatment against Cirrhosis (HALT-C) trial showed that peg-IFN alfa-2a maintenance therapy improved ALT level, HCV viral load, and necroinflammation.[93] Despite these benefits, no long-term benefit on the rate of disease progression and complications (cirrhosis, HCC, liver transplantation or mortality) was shown. A similar study, called the Colchicine Versus Peg-Intron Long Term (COPILOT) study (n=555), demonstrated that low-dose peg-IFN alfa-2b compared with low-dose colchicine (0.6 mg twice daily) resulted in similar clinical endpoints of liver failure, death, liver transplantation, variceal bleeding or HCC after 4 years of follow-up.[94] HCC was more commonly detected in peg-IFN treated patients (9% vs 4%), although complications of portal hypertension were observed less frequently in these patients (9% vs 14%).

Statement 22. In patients treated with peg-IFN alfa and ribavirin, treatment should be discontinued if: (Strong, High quality)

- **Early virologic response (EVR) is not achieved**
- **HCV RNA remains positive at treatment week 24 in genotype 1 patients.**

Treatment with combined peg-IFN and ribavirin can be used for 24 to 72 weeks in chronic hepatitis C, depending on response to therapy as monitored by HCV RNA testing and genotype. However, due to the cost, inconvenience and possible adverse effects of prolonged peg-IFN/ribavirin therapy, early identification of patients who will not respond is beneficial. Early virologic response, defined by at least a 2-fold $\log_{10}$ decrease in HCV RNA load after the first 12 weeks of treatment, is a reliable treatment-related predictor of SVR. The landmark trial of Fried et al on 1,121 chronic hepatitis C patients treated with peg-IFN/ribavirin found that of the 86% of patients who achieved EVR, 65% eventually achieved SVR.[37] In contrast, of the 14% who did not achieve EVR, 97% did not achieve SVR. Other studies confirmed that patients who did not reach EVR did not respond to further therapy beyond 12 weeks, concluding further that if treatment had been stopped in these patients, drug costs would have been reduced

by more than 20%.[95] Hence, early confirmation of viral reduction following initiation of antiviral therapy is worthwhile.

Another marker of treatment futility is detectable HCV RNA at 24 weeks of combined peg-IFN and ribavirin treatment. The large-scale trial by Manns et al showed that of the 403 patients who received peg-IFN/ribavirin and had detectable HCV RNA on week 24, only 1 patient (0.2%) achieved SVR.[36] Continued treatment of these patients to 48 weeks will not likely result in SVR and will only incur risks and costs for the patient.

Statement 23. In treatment-naïve patients on boceprevir-containing triple therapy, treatment should be discontinued if HCV RNA is ≥100 IU/mL at treatment week 12 (High quality, Strong) or detectable at week 24. (Moderate quality, Strong)

Statement 24. In re-treated patients on boceprevir-containing triple therapy, treatment should be discontinued if HCV RNA is >100 IU/ml at treatment week 12. (Moderate quality, Strong)

Due to the increased cost and adverse events secondary to triple treatment containing boceprevir, compared to dual therapy containing only peg-IFN and ribavirin, the importance of determining the likelihood of SVR with continued treatment is also important. Exploratory post hoc analyses of the data from SPRINT-2 (treatment-naïve) and RESPOND-2 (retreated patients) explored using detectable HCV RNA and HCV RNA of at least 100 IU/mL at 12 weeks as stopping rules for boceprevir-containing treatments.[96] The analyses showed that using detectable HCV RNA at week 12 would have possibly forfeited SVR in some patients, while using HCV RNA levels of at least 100 IU/mL almost universally predicted a failure to achieve SVR. The authors further concluded that in addition to the 12-week stopping rule stated, stopping treatment in those with detectable HCV RNA at week 24 maximized the early discontinuation of futile therapy and minimized premature treatment discontinuation.

Table 5 summarizes the recommended time points for HCV RNA determination during and after treatment, and its implications on treatment duration and discontinuation.

Acknowledgements:

The authors would like to thank and acknowledge the members of the Hepatology Society of the Philippines Hepatitis C virus consensus core group for their tireless dedication to this endeavor, as well as to the following societies and institutions whose representatives contributed greatly in the development of the consensus: Hepatology Society of the Philippines (HSP); Philippine Society of Gastroenterology (PSG); Philippine Society of Digestive Endoscopy (PSDE); Philippine College of Physicians (PCP); Philippine Society of Microbiology and Infectious Diseases (PSMID); and the Philippine Academy of Family Physicians (PAFP); and also to the following people who served as panelists and shared their knowledge and insight, and contributed magnanimously to the formation of these consensus statements: Mario Panaligan, MD; Rontgene Solante, MD; Eva Irene Maglonzo, MD; Jose Sollano Jr., MD; Evelyn Dy, MD; Alexander Uy, MD; Vanessa De Villa, MD; Digna Peňa, MD; Bernadette Moscoso, MD; Marigil Dofiles, MD; Erlinda Valdellon, MD; Roel Leonardo Galang, MD; Roberto Lopez, MD; Arsenio Co, MD; Mark Anthony De Lusong, MD; Benjamin Benitez Jr., MD; and Marilyn Arguillas, MD. Lastly, we acknowledge and thank Ivan Olegario, MD for his contributions in the preparation and writing of this manuscript.

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