

Project ECHO[®]

Hepatitis C Clinical Guidelines

This document is frequently edited to reflect current updates in treatment guidelines for Hepatitis C. Please access the document using the web link provided by ECHO staff. The link will connect you to the most recently updated version. If you do not have access to the link, please contact one of the ECHO administrators listed on the contact page. In order to minimize the need for tracking various paper versions, we advise against the printing of this document.

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- iii. [HCV Initial Presentation Form](#)
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- v. Project ECHO® HCV Clinic Contact Information:

[University of New Mexico, Albuquerque, NM](#)

[St. Joseph's Hospital, Phoenix, AZ](#)

[University of Washington School of Medicine, Seattle, WA](#)

[University of Utah School of Medicine, Salt Lake City, UT](#)

[St. Lukes Center for Liver Disease/Baylor College of Medicine, Houston, TX](#)

[Cherokee Nation W.W. Hastings Hospital, Tahlequah, OK](#)

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CONTRIBUTORS

Project ECHO® Hepatitis C Clinical Guidelines - Faculty Authors

Karla Thornton, MD, MPH

Professor of Medicine, Division of Infectious Diseases, University of New Mexico Health Sciences Center, Albuquerque, NM

Associate Director, Project ECHO®

Paulina Deming, PharmD

Associate Professor, College of Pharmacy, University of New Mexico Health Sciences Center, Albuquerque, NM

Clinical Pharmacist, Project ECHO®

Sanjeev Arora, MD

Professor of Medicine, Division of Gastroenterology, University of New Mexico Health Sciences Center, Albuquerque, NM

Director, Project ECHO®

Project ECHO® Hepatitis C TeleECHO® Team

Jill Gatwood, MS

Health Services Outreach Officer Project ECHO®

Scott Lockwood-Smith

Distance Education Coordinator, HCV Tele-ECHO® Clinics

Christie Carroll

Program Coordinator, HCV ECHO® Expansion Projects

Project ECHO® HCV Western States Consortium

John D. Scott, MD, MSc

Assistant Professor of Medicine/ Division of Allergy and Infectious Diseases, University of Washington/ Assistant Director of the Hepatitis and Liver Clinic at Harborview Medical Center Seattle, WA

Richard Manch, MD, FACP, FACG

Chief of Hepatology, Center for Liver and Hepatobiliary Disease, St. Joseph's Hospital and Medical Center/ Clinical Professor of Medicine, University of Arizona/ Professor of Medicine, Creighton University, Phoenix, AZ

Ann Moore, FNP

Project ECHO® Manager, Center for Liver and Hepatobiliary Disease, St. Joseph's Hospital and Medical Center, Phoenix, AZ

Terry D. Box, MD

Associate Professor of Medicine, Division of Gastroenterology/Hepatology, University of Utah Health Sciences Center, Salt Lake City, UT

Norman Sussman, MD

Associate Professor of Surgery, Baylor College of Medicine, St. Luke's Center for Liver Diseases, Houston, TX

Robert G. Gish, MD

Clinical Professor of Medicine, University of Nevada, Las Vegas, Senior Medical Director, St Joseph's Hospital and Medical Center, Liver Program, Phoenix, AZ

Jorge Mera, MD

Director, Infectious Diseases, Cherokee Nation W.W. Hastings Hospital, Tahlequah, OK

SCREENING FOR HCV INFECTION

A. Rationale for HCV Screening

In the United States, approximately 2.7-to 5 million patients are infected with chronic HCV infection.¹ Effective therapy is available for HCV and cure is achieved in a substantial proportion of patients who undergo therapy. Cure of HCV significantly reduces the patient's risk of developing cirrhosis, liver failure, liver transplant or hepatocellular cancer.

B. Recommendation for HCV Screening ([Attachment A](#))

Because most patients with chronic HCV do not have clinical symptoms related to their HCV infection, relying on clinical symptoms for screening is not recommended. Risk factors for infection include:

- Injection drug use
- Receipt of blood transfusion, blood products, or an organ transplant before 1992
- Shared personal care items, such as razors or toothbrushes, with a person who had hepatitis C
- Non-professional tattoo or body piercing
- Accidental needle stick injury
- Sex with an HCV-infected person
- Multiple sex partners or history of a sexually transmitted disease
- Mother with hepatitis C

In addition, per recent CDC recommendations and approval via United States Preventative Services Task Force, all persons born between 1945 and 1965 should have a one-time screening for HCV.² The rationale for testing all persons born during that birth cohort include a high rate of positivity among that group with estimates suggesting 75% of all HCV-positive adults were born between 1945-1965. Additional reasons for the recommendation include the impact of testing of reducing morbidity and mortality related to HCV infections, an overall lack of awareness of the HCV epidemic, and the advances in treatment.³

C. Initial HCV Screening with Antibody Testing

The HCV enzyme immunoassay (EIA) is the recommended initial screening test for HCV infection. Newer FDA-approved third generation EIA HCV antibody tests have a sensitivity and specificity greater than 99%. The EIA test determines whether the person has ever been infected with HCV, but it does not establish whether the patient has chronic (ongoing) infection or resolved infection. If initially negative, repeat HCV EIA testing should be performed annually if there is ongoing risk of infection. Given the sensitivity of the EIA, the recombinant immunoblot assay (RIBA) does not need to be performed for confirmation of HCV infection.

D. Confirmation of Positive Antibody Tests with Quantitative HCV RNA

Patients who have a positive HCV EIA should undergo quantitative HCV RNA testing to determine whether they have active or resolved HCV infection. Quantitative HCV RNA tests (e.g., COBAS® TaqMan® HCV Test) are highly sensitive (10-50 IU/mL) for the detection of viremia. Qualitative HCV RNA assays provide a detectable/non-detectable result, and although they are highly sensitive, they are no longer recommended. The HCV RNA level does not predict liver disease progression and should not be serially monitored to assess prognosis in persons not undergoing HCV treatment.

E. Follow-up for Patients who are HCV-Seropositive and HCV RNA Negative

A positive HCV antibody test followed by a negative HCV RNA assay may occur in several settings: (1) resolved HCV infection, (2) chronic infection with low-level viremia and transient undetectable HCV RNA, (3) acute infection with transient clearance of HCV RNA, and (4) a false positive HCV antibody test. Patients who are HCV seropositive and HCV RNA negative should have repeat HCV RNA tests performed in 4-6 months. If acute HCV is suspected (e.g., recent risk behaviors for infection), repeat testing should be performed in 8-12 weeks.

F. Indications for HCV RNA Testing in HCV-Seronegative Patients

Medical providers should perform quantitative HCV RNA testing in patients who have a negative HCV antibody test in persistently elevated alanine aminotransferase (ALT) levels in immunosuppressed patients. The rationale for performing HCV RNA testing in this setting is primarily based on the observation that false negative EIA HCV antibody tests occasionally occur among HIV-patients with severe immunodeficiency (CD4 count < 100 cells/mm³) or those receiving dialysis.

ROUTINE EVALUATION AND FOLLOW-UP OF PERSONS WITH CHRONIC HCV INFECTION

A. Baseline Studies in Persons with Established Chronic HCV

Patients identified as having chronic HCV infection (HCV RNA positive) should have the following baseline laboratory studies:

- Complete blood cell count
- INR (international normalized ratio)
- Comprehensive metabolic panel including serum creatinine, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, and serum albumin
- HCV Genotype and subtype
- Quantitative HCV RNA

- Hepatitis A serology (total or IgG)
- Hepatitis B serology (HBsAg, anti-HBs, anti-HBc)
- HIV Antibody

i. Routine Laboratory Studies

All patients with chronic HCV should be evaluated for severity of liver disease and degree of inflammation. The following laboratory abnormalities may be found in patients with cirrhosis: neutropenia, thrombocytopenia (<150,000 platelets/mL), prolonged INR, reversal of AST to ALT ratio, elevated bilirubin, low albumin. Elevated creatinine may be found in patients with HCV associated cryoglobulinemia.

ii. HCV Genotype

All patients with chronic HCV should undergo HCV genotype testing. There are 6 major HCV genotypes. In the United States, approximately 75% of persons infected with HCV have genotype 1; among African-Americans infected with HCV, the prevalence of genotype 1 is approximately 90%.⁴ For patients considering HCV treatment, genotype should be obtained because it provides valuable prognostic information with respect to treatment response. Subtyping of Genotype 1 is recommended.

iii. Quantitative HCV RNA

The quantitative HCV RNA level provides prognostic information related to treatment response, but does not correlate with the degree of liver inflammation or fibrosis. Of historical interest, a HCV RNA level greater than 400,000 IU/ml is associated with a poorer response to treatment with pegylated interferon and ribavirin.

iv. Hepatitis A and B Virus Serologies

All HCV-infected persons should be screened for immunity with HAV antibody (total or IgG), hepatitis B surface antibody (anti-HBs), and hepatitis B core antibody (anti-HBc). More information on hepatitis B serologic testing can be found at

www.cdc.gov/hepatitis/HBV/PDFs/SerologicChartv8.pdf⁵

Table 1: Interpretation of Hepatitis B serologies

Tests	Results	Interpretation
HBsAg Anti-HBc Anti-HBs	Negative Negative Negative	Susceptible to HBV
HBsAg Anti-HBc Anti-HBs	Negative Positive Positive	Previous exposure to HBV with the presence of antibody. These patients are not immune or “protected” and frequently have subclinical infection and are at risk for reactivation with immunosuppression.
HBsAg Anti-HBc Anti-HBs	Negative Negative Positive	Immune due to previous HBV vaccine exposure
HBsAg Anti-HBc IgM anti-HBc Anti-HBs	Positive Positive Positive Negative	Acute HBV infection
HBsAg Anti-HBc IgM anti-HBc Anti-HBs	Positive Positive Negative Negative	Chronic HBV infection
HBsAg Anti-HBc Anti-HBs	Negative Positive Negative	Four possible interpretations: <ol style="list-style-type: none"> 1. Resolved infection 2. False positive anti-HBc, susceptible to HBV infection 3. Low level chronic infection 4. Resolving acute infection <p>The presence of anti-HBc with or without anti-HBs, indicates that these patients are not immune or “protected” and frequently have subclinical infection and are at risk for reactivation with immunosuppression</p>

v. HIV Testing

Because HIV and HCV infections share common routes of transmission, patients with HCV should be screened for HIV.

vi. IL-28B Testing

IL-28B testing is optional and not routinely recommended. Genetic polymorphisms near the IL28B gene, which encodes for interferon lambda, have been shown to correlate with treatment response in genotype 1 HCV infection. Specifically, the CC genotype is associated with increased spontaneous clearance and higher rates of cure than with either the CT or TT genotypes.⁶ The Interleukin 28B Polymorphism (IL28B) GenotypeTest is currently available through LabCorp. The test can be performed on a buccal swab or whole blood sample. This test is being obviated with the new all oral therapy algorithms.

vii. NS3 Q80K Polymorphism Testing

The manufacturer of simeprevir recommends testing patients with HCV genotype 1a for the Q80K polymorphism prior to undergoing treatment with simeprevir due to the markedly reduced response rate in patients with this mutation. The test is available through LabCorp (HCV Genosure Drug Resistance Assay NS34A) and Quest (HCV Viral RNA NS3 Genotype). Patients who are positive for the Q80K polymorphism should not be treated with simeprevir, PEG-IFN, and ribavirin. The relevance of this polymorphism is diminished when simeprevir is used in combination with sofosbuvir. We do not recommend testing for this polymorphism in patients receiving dual therapy with simeprevir/sofosbuvir.

viii. Screening for Other Causes of Liver Disease

In some patients, other causes of liver disease may be considered including:

- Wilson's Disease
- Hemochromatosis
- Autoimmune Hepatitis
- NASH

For more information regarding the diagnosis and management of these conditions, see the following AASLD practice guidelines: <http://www.aasld.org/practiceguidelines/Pages/default.aspx>

ix. Liver Biopsy

Liver biopsy may be considered in some patients but is not required prior to treatment. Liver biopsy provides information regarding the intensity of the liver inflammation (how active is the hepatitis) and the degree of fibrosis (how much long-term damage has occurred).

B. Vaccinations

Patients with chronic HCV should avoid becoming newly infected with either HAV or HBV. All patients without immunity should be vaccinated. Additionally, all patients with chronic liver disease, including ongoing alcoholism, should receive the pneumococcal vaccine.⁷

C. Assessment and Management of Alcohol and Substance Use

All patients with chronic HCV should be counseled regarding their alcohol and drug use, including marijuana, tobacco, and prescription medication abuse. Alcohol use can accelerate the progression of

liver disease, diminish the response to therapy, and exacerbate the risks of therapy.^{8, 9} Marijuana use has been shown to increase fibrotic changes.¹⁰ Cigarette smoking potentiates liver damage, increases the risk for HCC, and increases the risk of infection during therapy. Importantly, patients should not be excluded for treatment of HCV based on a past history of alcohol or drugs.

D. Evaluating and Modifying Obesity

Obesity is associated with the development of nonalcoholic fatty liver disease and hepatic steatosis, which can accelerate the progression of HCV-related liver disease.¹¹ In addition, obesity-associated insulin resistance may diminish the response to HCV therapy. Overweight patients (defined as a BMI of > 25 kg/m²) should receive counseling on weight reduction, including formal counseling by a dietician and, referral to a weight reduction program, if available.¹²

E. Monitoring for Hepatocellular Cancer

Patients with chronic HCV infection and advanced fibrosis/cirrhosis have an increased risk of developing hepatocellular cancer (HCC). The incidence of HCC is estimated to be 2% to 8% per year. These individuals should have surveillance for HCC with hepatic ultrasound every 6 months.¹³ Any suspicious lesions may require additional evaluation with a multi-phase contrast abdominal computed tomographic (CT) scan or a magnetic resonance imaging (MRI) study. Due to limited accuracy, alpha-fetoprotein (AFP) is considered an inadequate test for surveillance for HCC and is not recommended alone without ultrasound. Routine surveillance every 6 months with ultrasound and AFP has been shown to reduce HCC related mortality by 37%.¹⁴ Routine surveillance for HCC in persons with chronic HCV but without F3/ F4 cirrhosis is not recommended. Although rare, patients with cirrhosis who are cured of HCV infection may still develop HCC and should continue to have routine surveillance. Surveillance in patients with stage 3 fibrosis is optional and not yet part of guidelines.

F. Evaluation for Cirrhosis-Related Complications

In addition to monitoring for HCC, patients with cirrhosis should undergo evaluation for and management of any cirrhosis-related complications. Specifically, history and physical examination should evaluate the patient for encephalopathy and/or ascites. Patients with cirrhosis should undergo endoscopy to evaluate for the presence of esophageal varices to determine the need for banding and prophylaxis with a nonselective beta blocker (such as nadolol or propranolol). **For detailed and additional information see the following AASLD guidelines: [Prevention and Management of Gastroesophageal Varices and Variceal Hemorrhage in Cirrhosis](#)**

G. Indications for Referral to Hepatologist and for Liver Transplantation

Patients with cirrhosis should periodically have assessment of their liver status with a validated prognostic model, such as the Model for End-Stage Liver Disease (MELD) score which includes the patient's serum creatinine, total bilirubin and INR and can be calculated using online resources such as the Mayo Clinic: <http://www.mayoclinic.org/meld/mayomodel6.html>. The model can predict mortality risk and serves as an indicator for liver transplantation referral.¹⁵

H. Ongoing Monitoring of Patients Not on HCV Therapy

Patients with chronic untreated HCV or those who have failed HCV treatment should be followed regularly for their liver disease. Patients should limit their intake of acetaminophen to less than 2 grams/day, abstain from alcohol and marijuana use, and maintain a normal body mass index (< 25 kg/m²). Additionally, patients with cirrhosis should avoid non-steroidal anti-inflammatory drugs (NSAIDs). Patients should be reevaluated on a regular basis for consideration of HCV treatment.

I. Patient Education ([Attachment B](#))

See attachment B.

PATIENTS WITH ESTABLISHED HCV INFECTION: EVALUATION FOR THERAPY

A. Goals and rationale for HCV Treatment

The goal of HCV treatment is viral eradication. Successful treatment of HCV can result in decreased risk of developing cirrhosis, end-stage liver disease, and HCC. Additionally viral eradication eliminates the risk of transmission of HCV to others. The benefits of therapy include reduction in progression of fibrosis and HCV related complications.

B. Treatment Response Terminology

Sustained virologic response (SVR) was previously defined as an undetectable HCV RNA in serum 24 weeks after completing HCV therapy; patients who achieve SVR have a very high likelihood of achieving a long-term cure of HCV.¹⁶ Clinical trial data using sofosbuvir and simeprevir defined SVR at 12 weeks after the end of treatment. It is anticipated that this will be the accepted standard for the definition of SVR. Other terms used in defining response to treatment include the following:

- End of Treatment Response (ETR): undetectable viral load by the end of treatment
- Relapser: patient who achieves an ETR but who has a detectable viral load after treatment is completed
- Partial responder: for patients on treatments with IFN/RBV treatment only - a patient who achieves a ≥ 2 log drop in viral load but whose viral load never becomes undetectable
- Null-responder – for patients on treatments with IFN/RBV treatment only: a patient who does not achieve a ≥ 2 log drop in viral load at week 12 of treatment

C. Baseline Factors Predicting Response

The following factors are associated with a decreased response to HCV treatment with pegylated interferon and ribavirin: Genotype 1

- HCV RNA >400,000 IU/mL
- African American race
- Bridging fibrosis or cirrhosis
- Body weight > 75 kg
- Insulin resistance
- Normal ALT (≤ 30 IU/L in males and ≤ 19 IU/L in females)
- IL-28B genotype TT or CT

The relevance of risk factors is markedly diminished with newer therapies. Patients with fibrosis and cirrhosis and/or who are African American continue to have reduced responses to treatment. Historically genotype 1 was the most difficult to treat genotype however as therapy evolves, genotype 3 is proving to be the more difficult genotype. The NS3 Q80K mutation results in substantial reductions of simeprevir efficacy for patients with HCV genotype 1a infections.

D. Mental Health Assessment ([Attachment D](#))

Mental health screening prior to initiating HCV therapy is recommended for multiple reasons. Patients infected with HCV have increased rates of depression.^{17,18} In addition, active and untreated mental health issues can interfere with adherence to HCV treatment. A baseline evaluation can be helpful in identifying pre-existing issues and also as a barometer if psychiatric issues develop during HCV therapy. We recommend the use of the Patient Health Questionnaire (PHQ-9), a standardized depression screening tool, before and during HCV treatment. Family and social support issues should be explored to prepare the patient for the challenges of treatment and improve patient adherence to therapy.

Depression and other psychiatric illnesses may worsen during interferon-based treatment. There are insufficient data to suggest the routine use of antidepressants for all patients considered for HCV treatment. Given the rapid and effective response of antidepressants to treat IFN-induced depression, there is no indication for routine prophylaxis of all patients.¹⁹ The prophylactic use of antidepressants should be reserved for patients with a current history of depression or anxiety disorders or for patients with a prior history of IFN-induced depression. Moreover, the reduced duration of IFN-based therapy will likely decrease the incidence of IFN-induced depression.

E. Substance Abuse Assessment

Patients should be evaluated for alcohol, illicit drug use, prescription drug abuse, and marijuana use prior to initiating HCV therapy. The use of a standardized assessment tool such as AUDIT (The Alcohol Use Disorders Identification Test) is optional. Patients with extensive substance abuse histories may require formal rehabilitation programs prior to initiating treatment. Alcohol abstinence is required and willingness to abstain from alcohol should be verified prior to initiation of therapy. Patients should abstain from the use of marijuana.

F. Assessment of Medical Comorbidities

All medical comorbid conditions should be optimally managed prior to starting HCV therapy. Prior to starting therapy, a thorough medical history should be obtained. If the following pre-existing conditions are observed, the following examinations should be obtained:

If there is evidence of cirrhosis, obtain a baseline abdominal ultrasound for HCC screening and an EGD for evaluation of esophageal varices.

If the patient is diabetic, a retinal exam should be documented within the last 12 months.

The following additional examinations should be considered:

- Cardiology consult or stress testing - if known CAD (Coronary Artery Disease) or high risk for CAD
- Pulmonary function test – if known lung disease
- Dental Exam – if evidence of poor dentition

G. Contraindications for Interferon Based HCV Therapy:

- Decompensated cirrhosis
- Albumin < 3.5 and Platelets < 100,000/mm²⁰
- Active substance use
- Inability to cooperate with treatment
- Uncontrolled psychiatric condition
- Suicidal behavior within the past 12 months
- Severe concurrent medical disease (such as uncontrolled diabetes, significant ischemic heart disease, obstructive pulmonary disease)
- Active, untreated autoimmune disease
- Uncontrolled hyper/hypothyroidism

Although clinicians should make a strong effort to treat all HCV infected patients, some patients should not receive HCV therapy because the risk of treatment clearly outweighs the potential benefit. Effort to overcome the contraindications should be made whenever possible.

H. Contraindications for the Use of Ribavirin

- Women who are pregnant, nursing, or not able to practice contraception

I. Overcoming Barriers to Initiating Treatment

Clinicians should formally address any barrier that exists that interferes with the patient's ability to undergo HCV treatment including treatment programs for alcohol and substance abuse and mental health counseling. Patients are often not willing to undergo HCV treatment due to misinformation or valid concern of possible side effects. It is important to develop appropriate patient education, including consideration of peer based or group-based counseling, to improve treatment acceptance rates.

J. Reevaluating For Treatment

Patients who are either unwilling or unable to undergo HCV therapy should undergo reevaluation for HCV therapy on an annual basis. In addition, as new treatments become available, treatment decisions should be reconsidered.

K. Adherence to Treatment

Adherence to HCV treatment is critical for response. Predictors of poor adherence include the presence of psychological problems, complexity of treatment, and side effects of medication.²¹ Additionally, adherence is markedly reduced with increased frequency of medication dosing. Known barriers to adherence include patient-provider communication including a patient's poor understanding of the disease state, the risks and benefits of treatment, and a lack of understanding of how to take the medication.

Treatment of HCV involves multiple factors known to affect adherence and because adherence is crucial for optimal response, all patients should be thoroughly evaluated prior to initiation of treatment and educated about the risks and benefits of treatment. Patients not currently approved for therapy should be encouraged to resolve the underlying obstacles to therapy in preparation for therapy so that therapy can be initiated with the greatest likelihood for success.

There are no reliable markers to predict optimal adherence. Higher socioeconomic status, degree of education, and a lack of drug abuse history do not predict optimal adherence. Instead, all patients should be evaluated for readiness to start therapy, provided with a thorough understanding of their disease state including anticipating side effects and the impact of non-adherence, and offered emotional and practical support to manage their medication including suggestions for improving the convenience of the regimen and given educational tools such as pictures, pill boxes, or calendars. Adherence is improved with a team approach- engage family, friends, and other healthcare workers such as nurses, pharmacists, and peer counselors. Patients who have access to a health care team they trust are more likely to adhere to treatment.

INITIATING HCV THERAPY

A. Pre-treatment Work-up

i. Baseline Laboratory Studies Prior to Starting Therapy.

Obtain the following labs within 60 days of starting treatment to establish the baseline (week 0):

- CBC with differential
- Chem 7
- Liver enzymes ALT, AST, alkaline phosphatase
- Liver function tests: albumin, total and direct bilirubin, INR
- Fe, TIBC, ferritin

- Vitamin D 25-OH
- TSH (for those receiving interferon)
- Urine or serum pregnancy test (women of childbearing capacity)
- Alpha fetoprotein (if cirrhosis)
- Hgb A1C (if diabetic)
- HIVRNA and CD4 count (if HIV infected)

The following labs should be current within past 12 months:

- HCV-RNA Quant

Patients must have documentation of the following labs:

- HCV Genotype and subtype
- HBsAg, anti-HBs, anti-HBc, HAV Ab
- HIV Ab

ii. Vitamin D Replacement

- For 25 OH Vitamin D level < 20ng/ml give Vitamin D3 50,000 units PO every week for 8 weeks then 2,000 units daily for one month.
- For 25 OH Vitamin D level ≥ 20ng/ml but < 40ng/ml give Vitamin D3 2,000 units PO every day.
- Repeat 25 OH Vitamin D level after 3 months.

B. Patient Education ([Attachment B](#))

Patients should be educated about all aspects of HCV treatment including potential duration of therapy, side effects, and medication adherence challenges.

C. Treatment for Persons with Acute HCV

Among patients who develop acute HCV infection, approximately 20% will have spontaneous resolution of the HCV; the spontaneous resolution is often evident within 12 weeks after infection, but some patients have a more delayed clearance. As a result, it is reasonable to defer HCV treatment for 12 weeks after the detection of HCV antibody and HCV RNA.²² Patients with acute HCV present a unique treatment opportunity since SVR rates are substantially higher with treatment of acute HCV than chronic HCV.²³ There are currently no guidelines regarding the use of direct acting antivirals for acute HCV.

D. Treatment Currently FDA Approved for Persons with Chronic HCV

The current treatment depends on HCV genotype. The duration of therapy varies from 12 weeks to 48 weeks. Monotherapy with ribavirin, sofosbuvir, or a protease inhibitor is not appropriate.

i. FDA Approved Treatments

For HCV Genotype 1:

- Sofosbuvir + PEG-IFN + Ribavirin x 12 weeks
- Sofosbuvir + Ribavirin x 24 weeks
- Protease Inhibitor (simeprevir, boceprevir, or telaprevir) + PEG-IFN + Ribavirin for 24-48 weeks based on response

For HCV Genotype 2:

- Sofosbuvir + Ribavirin x 12 weeks
- PEG-IFN + Ribavirin x 24 weeks

For HCV Genotype 3:

- Sofosbuvir + Ribavirin x 24 weeks
- PEG-IFN + Ribavirin x 24 weeks

For HCV Genotype 4:

- Sofosbuvir + PEG-IFN + Ribavirin x 12 weeks
- PEG-IFN + Ribavirin x 48 weeks

ii. FDA Approved Medications

Pegylated Interferon:

Two forms of PEG-IFN have been developed and studied in large clinical trials: peginterferon alfa-2a (Pegasys®) and peginterferon alfa-2b (PEGIntron®). These two products are similar in efficacy and safety, but have different dosing regimens.

Pegasys®: fixed dose of 180 micrograms (mcg) subcutaneously once per week.

PEGIntron®: weight-based dose of 1.5 mcg per kilogram subcutaneously once per week.

Ribavirin:

Ribavirin is an oral medication . It is dosed twice a day for a total daily dose based upon body weight:

- <75 kg 1000mg/qd
- ≥75 kg 1200mg/qd

Several products of ribavirin are available as 200 mg tablets including Copegus® and RibaTab®, and as a 200 mg capsule, Rebetol®. The Ribasphere® RibaPak® is a prepackaged 2-tablet dosing product available as an 800 mg, 1000 mg, or 1200 mg daily dose.

Protease Inhibitors:

Currently three protease inhibitors, simeprevir, boceprevir and telaprevir, are available for genotype 1 infections and are used in conjunction with PEG-IFN and ribavirin.

- Simeprevir: oral medication given 150 mg once daily with food
- Boceprevir: oral medication given 800 mg every 8 hours with food or snack.
- Telaprevir: oral medication given 750 mg every 8 hours with food containing a minimum of 20 grams of fat

Polymerase Inhibitors:

- Sofosbuvir is a polymerase inhibitor with antiviral activity against HCV genotypes 1, 2, 3, and 4. It is available as a 400mg oral tablet dosed once daily.

E. Choice of Regimen and Duration of Therapy

i. Recommendation for genotype 1 infection:

- See Genotype 1 decision tree ([Attachment G](#)). Rationale for choice and duration of regimen:

For patients who are naïve to therapy or relapsers we recommend sofosbuvir + pegylated interferon + ribavirin for 12 weeks. This combination was evaluated in the NEUTRINO trial and is expected to result in an SVR12 of 92% in patients without cirrhosis and 80% in patients with cirrhosis.²⁴ This preferred treatment is consistent with the recommendation for therapy in the joint AASLD and IDSA guidelines for HCV therapy.²⁵

For interferon ineligible/intolerant patients and patients who were null or partial responders to previous interferon based therapy we recommend a combination of sofosbuvir + simeprevir + ribavirin for 12 weeks. If this combination cannot be obtained a combination of sofosbuvir + ribavirin for 24 weeks can be considered.

The COSMOS study evaluated the efficacy of sofosbuvir with simeprevir plus or minus ribavirin. The study enrolled patients with advanced disease (patients with fibrosis stage 3 or 4, n=87) and preliminary results indicate SVR4 was 93%.²⁶ The outcomes for SVR12 are not yet available but given the high efficacy rate, it is reasonable to consider this alternative regimen in patients unable to tolerate interferon. Although not statistically significant, the cure rate for patients who received ribavirin was higher. We believe ribavirin should be used unless there is a contraindication.

Sofosbuvir based regimens are the preferred choice for genotype 1 infection because of high SVR rates and shorter duration of treatment. In the event there is a contraindication to sofosbuvir or sofosbuvir cannot be obtained, a regimen containing simeprevir, pegylated interferon and ribavirin can be considered. A test for the Q 80 K mutation must be performed prior to using simeprevir in HCV genotype 1 A patients.²⁷

Patients without advanced liver disease or severe extra hepatic manifestations should consider waiting for newer therapies.

ii. Recommendation for genotype 2 infection:

- Sofosbuvir + ribavirin for 12 weeks. Rationale for choice and duration of regimen:

The combination of sofosbuvir and ribavirin was evaluated in 3 clinical trials and is expected to achieve an SVR of 94%.^{24,28,29} This treatment combination is consistent with that of the joint AASLD and IDSA guidelines for HCV therapy.²⁵

iii. Recommendation for genotype 3 infection:

- Sofosbuvir + ribavirin for 24 weeks. Rationale for choice and duration of regimen:

The overall response in genotype 3 patients is expected to be greater when the therapy is extended to 24 weeks and estimated to have an SVR12 of 84%.^{24,28,29}

Patients who are cirrhotic and non-responders to previous HCV therapy have a lower SVR at 60% when given 24 weeks of sofosbuvir and ribavirin. A combination of sofosbuvir + pegylated interferon + ribavirin for 12 weeks should be considered for non-responder cirrhotics. In a small trial this combination improved SVR rates to 83%.³⁰

iv. Recommendation for genotype 4 infection:

- Sofosbuvir + pegylated interferon + ribavirin for 12 weeks.

Based on the NEUTRINO trial in a small number of patients (n=28), this combination therapy is expected to result in an SVR of 96%. This therapeutic regimen is consistent with the joint recommendations of the AASLD and IDSA for HCV therapy.

Patients without advanced liver disease or severe extra hepatic manifestations should consider waiting for newer therapies.

v. Special Populations

- HIV Coinfection

Patients with HIV-HCV coinfection should be treated according to HCV mono-infection recommendations. Sofosbuvir is indicated for use in patients with HIV-HCV coinfection. Sofosbuvir was administered in combination with multiple HIV antiretrovirals and no significant drug-drug interactions were noted. Efficacy was high with SVR rates comparable to HCV mono-infected patients. For HIV-coinfected patients who receive a regimen which contains simeprevir, the potential for drug interactions must be carefully considered. (see drug interaction section below).

- Patients Awaiting Liver Transplant

Sofosbuvir is approved in combination with ribavirin for treatment of chronic HCV in patients with hepatocellular carcinoma awaiting liver transplantation for up to 48 weeks or until liver transplantation, whichever occurs first.

F. How To Obtain Treatment Medications

Patient assistance programs exist for all currently available HCV medications. ([Attachment C](#))

G. Common Side Effects

Side effects related to peginterferon/ribavirin occur in nearly all patients; however, the severity and nature of these toxicities is highly variable in treated individuals. Most commonly seen side effects are listed in table that follows.

Table 2: Common Side Effects with Pegylated Interferon, Ribavirin, Protease Inhibitors and Polymerase Inhibitors

Common Side Effects					
Pegylated Interferon and Ribavirin		Protease Inhibitors			Polymerase Inhibitors
PEG-IFN	RIBAVIRIN	SIMEPREVIR	BOCEPREVIR	TELAPREVIR	SOFOSBUVIR
Flu-like symptoms: fever, headache, myalgia Fatigue Depression Irritability Insomnia Nausea Vomiting Anorexia Cognitive dysfunction	Rash Fatigue Nausea Vomiting	Rash including photosensitivity Pruritus Nausea	Fatigue Nausea Headache Dysgeusia	Rash Anorectal symptoms: hemorrhoids, anal pruritus, anal discomfort	Headache Fatigue

H. Drug-Drug Interactions

A useful website for drug interactions is: <http://www.hep-druginteractions.org/Interactions.aspx>

- Simeprevir: There are multiple drug interactions with simeprevir and various other medications. Although many of these interactions can be managed, the following table lists known medications which should *not* be coadministered with simeprevir:

Table 3: Known Drug Interactions with Simeprevir (Co-Administration Not Recommended)

Drug Class/ Drug Name	Effect	Recommendation
Anticonvulsants		
Carbamazepine; Phenytoin; Phenobarbital; Oxcarbazepine	Decreases simeprevir	Do not coadminister
Antibiotics		
Erythromycin; Clarithromycin; Telithromycin	Increases simeprevir	Do not coadminister
Antifungals (systemic)		
Itraconazole; Ketoconazole; Posaconazole; Fluconazole; Voriconazole	Increases simeprevir	Do not coadminister
Antimycobacterials		
Rifampin, Rifabutin, Rifapentine	Decreases simeprevir	Do not coadminister
Corticosteroids (systemic):		
Dexamethasone	Decreases simeprevir	Do not coadminister
Herbals		
St. John's wort	Decreases simeprevir	Do not coadminister
Milk Thistle	Increases simeprevir	
HIV Meds:		
Cobisistat-containing products; Efavirenz; Delavirdine, etravirine, nevirapine; Darunavir/ritonavir; Ritonavir; Atazanavir, fosamprenavir, lopinavir, indinavir, nelfinavir, saquinavir, tipranavir	Various effects	Do not coadminister

Table 4: Use of HMG CO-A Reductase Inhibitors ("Statins") with Simeprevir ³⁵

Statin Drug	Effect	Recommendation
Rosuvastatin	Increased rosuvastatin	Start rosuvastatin at 5 mg, do not exceed 10 mg when co-administered with simeprevir

Atorvastatin	Increased atorvastatin	Use lowest necessary dose, do not exceed 40 mg when co-administered with simeprevir
Simvastatin	Increased simvastatin	Use lowest possible dose with co-administered with simeprevir
Pitavastatin Pravastatin Lovastatin	Increased levels of statin	Use lowest possible dose with co-administered with simeprevir

Table 5: Use of Immunosuppressants with Simeprevir

Immunosuppressant	Effect	Recommendation
Cyclosporine	Increased cyclosporine	Monitor cyclosporine concentrations; no dose adjustment required
Tacrolimus	Decreased tacrolimus	Monitor tacrolimus concentrations; no dose adjustment required
Sirolimus	Increased or decreased sirolimus	Monitor sirolimus concentrations; no dose adjustment required

- Sofosbuvir:

Table 6: Known Drug Interactions with Sofosbuvir (Co-Administration Not Recommended)

Drug Class/ Drug Name	Effect	Recommendation
Anticonvulsants		
Carbamazepine; Phenytoin; Phenobarbital; Oxcarbazepine	Decreased sofosbuvir	Do not coadminister
Antimycobacterials		
Rifabutin; Rifampin; Rifapentine	Decreased sofosbuvir	Do not coadminister
Herbals		
St. Johns wort	Decreased sofosbuvir	Do not coadminister
HIV Protease Inhibitors		
Tipranavir/ ritonavir	Decreased sofosbuvir	Do not coadminister

A number of drugs were evaluated and have no significant drug interaction. The following may be safely used in patients undergoing sofosbuvir therapy:

- Cyclosporine
- Tacrolimus
- Methadone
- Darunavir/ritonavir
- Efavirenz
- Emtricitabine

- Raltegravir
- Rilvirine
- Tenofovir DF

I. Common Laboratory Abnormalities

i. Pegylated Interferon, Ribavirin, and Protease Inhibitors

Hemolytic anemia is an expected effect of ribavirin exposure and may cause subclinical elevations in uric acid. Interferon is known to cause bone marrow suppression and resulting in various laboratory abnormalities. The most common laboratory abnormalities are listed in the table below:

Table 7: Common Laboratory Abnormalities with peg-IFN, Ribavirin, and Protease Inhibitors

Pegylated Interferon and Ribavirin		Protease Inhibitors		
PEG-IFN	RIBAVIRIN	SIMEPREVIR	BOCEPREVIR	TELAPREVIR
Neutropenia	Anemia	Transient elevations in bilirubin	Anemia	Anemia
Thrombocytopenia	Subclinical elevations of uric acid	Subclinical elevations of alkaline phosphatase	Neutropenia	Subclinical elevations of uric acid
Lymphopenia				Transient elevations in bilirubin
Anemia				
Autoimmune thyroiditis- hyper or hypothyroid				
Elevated or increasing liver enzymes or liver dysfunction				

ii. Polymerase Inhibitors

Sofosbuvir is associated with few laboratory abnormalities. When combined with other therapeutic agents, the most common abnormalities reflect those abnormalities associated with the other therapeutic agents.

J. Additional Drug Information

i. Complementary and Alternative Medicine Therapies for HCV:

Complementary and alternative medicine (CAM) therapies are used by a substantial number of persons with chronic HCV infection, with some surveys estimating in excess of 20% of patients with chronic HCV using at least one CAM therapy. The most commonly used alternative medicine is Silybum marianum, commonly referred to as silymarin or milk thistle. Other agents used include echinacea, St. John's wort, valerian, and ginkgo biloba. Milk thistle is a known drug interaction for simeprevir, expected to reduce the efficacy of simeprevir and should be avoided during HCV therapy. Similarly, St. John's wort should not be used during any HCV therapy as this herb has multiple known drug-drug interactions and is expected to decrease the therapeutic efficacy of many drugs including sofosbuvir and simeprevir. Thus, clinicians should ask patients about their use of "natural medications", including herbal products, vitamins, and supplements.

Although CAM therapies are frequently used, there are no data to support their use for patients with chronic HCV infection. In addition, alternative medications have the potential to interfere or interact with traditional therapies used to treat HCV. The use of St. John's wort is contraindicated with sofosbuvir and Simeprevir. At present, the use of complementary medications is not recommended for patients with HCV. Moreover, some herbal products can pose additional risks to patients with cirrhosis because of effects on platelets and clotting ability.

CAM Recommendations:

- Patients who are candidates for hepatitis C therapy should stop all herbal supplements while on therapy.
- Patients who have cirrhosis who want to take herbal supplements should be counseled on the potential complications of using herbals. All herbal supplements in patients with cirrhosis should be evaluated for potential increased risk of bleeding.

ii. Drugs to Avoid in Patients with Liver Disease

- Antidepressants: Many antidepressants are extensively metabolized by the liver and can accumulate due to impaired metabolic activity. In general, antidepressants should be started at a lower dose and titrated up for effect. Duloxetine should not ordinarily be used due to reported cases of fatal hepatic failure.
- Benzodiazepines: The use of benzodiazepines should be evaluated in all patients due to concerns for abuse and the risk of over-sedation. Although all benzodiazepines are metabolized by the liver, lorazepam, oxazepam, and temazepam are metabolized through a pathway typically preserved even in patients with cirrhosis and have no dosage adjustment recommended in patients with liver disease. Alprazolam has altered metabolism in liver disease and can accumulate despite its short action of activity; therefore it should be used with caution. Chlordiazepoxide, clonazepam, and diazepam are all long-acting benzodiazepines known to accumulate in patients with liver disease and should be avoided in chronic use.
- OTC Pain Management: Acetaminophen and NSAIDs: Acetaminophen may be used in cirrhotic patients with a maximum use of 2 grams daily for no longer than 14 days at a time.

Acetaminophen induced hepatotoxicity is a well-known cause of hepatic failure and often occurs due to unintentional overdosage. Moreover, even among healthy patients LFTs can increase to 3x the upper limit of normal at a dose of 4 grams daily for 14 days with complete resolution when acetaminophen is stopped.³¹ (Patients should be counseled on the prevalence of acetaminophen in many OTC products and limit use. Patients with on-going pain management issues should be considered for alternative pain treatment. NSAIDs including aspirin, ibuprofen, naproxen, and others should be avoided in patients with cirrhosis due to an increased risk of bleed, potential for renal toxicity, and impaired response to diuretic therapy.^{32, 33,34}

- Statins: Although statins are rarely associated with elevations in liver enzymes, there are currently no data to suggest statins should be avoided in patients with liver disease, including patients with HCV. No difference in AST/ALT elevations has been found among HCV seropositive or HCV seronegative patients. Additionally, patients with compensated cirrhosis are not known to experience an increase in statin related hepatotoxicity.³⁵ There are no known drug-drug interactions with sofosbuvir and statins. Statins may be used with simeprevir but require lower dosages and monitoring for safety; increased levels of statins pose a risk for rhabdomyolysis.
- Phosphodiesterase Inhibitors (sildenafil, tadalafil, vardenafil): The use of these agents for erectile dysfunction should be started at the lowest effective dose in patients with cirrhosis and titrated to effect. Individual drug-drug interactions vary.

MONITORING OF PATIENTS WHO RECEIVE HCV THERAPY

A. Planned Laboratory Studies and Visits During Therapy (Click on the links below)

- [Sofosbuvir/ Ribavirin Flow Sheet](#)
- [Sofosbuvir/ Peginterferon/ Ribavirin Flow Sheet](#)
- [Sofosbuvir/Simeprevir Flow Sheet](#)

B. Pregnancy and Birth Control

Ribavirin can cause birth defects and fetal death. Pregnant women and men whose female partners are pregnant or considering pregnancy are not candidates for therapy. Patients must practice 2 forms of birth control during treatment and for 6 months after. Simeprevir does not affect ethinyl estradiol/norethindrone concentrations. There are no data regarding the effects of sofosbuvir on hormonal contraceptives. The current manufacturer recommendations state that 2 forms of non-hormonal contraception should be used and that female patients should have a negative pregnancy test prior to initiating therapy and monthly thereafter.

C. Treatment Algorithms

(Click on the links below)

- [Sofosbuvir Genotype 1 Algorithm](#)
- [Sofosbuvir Genotype 2 Algorithm](#)
- [Sofosbuvir Genotype 3 Algorithm](#)
- [Sofosbuvir Genotype 4 Algorithm](#)

D. Management of Common Systemic Symptoms

i. Influenza-like Symptoms

Interferon injections are associated with an “influenza-like” illness that may include fever, headache, myalgia and arthralgia. The onset of symptoms is approximately 4 to 6 hours after the injection and may persist for several days. Although symptoms tend to be self-limited, management includes the use of either NSAIDs or acetaminophen. Patients who continue to work while on therapy should consider administering injections immediately prior to any time off to offset the impact symptoms may have on productivity.

ii. Fatigue

The incidence of fatigue is high (up to 90%) and may be due to several factors including depression, anemia, or hypothyroidism. Neuropsychiatric and neurovegetative effects can be managed with antidepressants with combined serotonin and norepinephrine activity including bupropion or venlafaxine. Exercise is also an effective tool for managing symptoms.

iii. Rash

Ribavirin and simeprevir can cause rash and management of rash is similar. For mild to moderate rash, patients may be treated with oral antihistamines and topical corticosteroids. Additionally, patients should be counseled on good skin care practices including the use of emollients and be advised to refrain from UV exposure. Patients who develop rash should be followed for progression of rash to mucosal or systemic symptoms. Photosensitivity in patients treated with simeprevir was also reported in an exaggerated sunburn exposure typically affecting the face, neck, surfaces of forearms, and dorsa of hands. Patients should limit sun exposure, use sun protective measures, and avoid tanning.

- Sulfa allergy: simeprevir does contain a sulfonamide moiety. No increased incidence of rash or photosensitivity was observed in patients with a history of sulfa allergy. All patients with a history of sulfa allergy who will be treated with simeprevir should be counseled on risk of rash and monitored for rash development.

iv. Headache

Some patients treated with sofosbuvir can develop headaches. Management may include OTC pain medications such as acetaminophen or NSAIDs including aspirin.

E. Management of Depression

i. Monitoring for Depression during Interferon Based Treatment

Interferon induced depression occurs in up to 50% of patients.³⁶ Moreover, risks for IFN-induced depression include severity of depression at baseline and the duration of IFN therapy. The exact etiology of IFN induced depression is unknown, however, IFN is known to deplete tryptophan, a serotonin precursor.³⁷ Patients should be carefully observed and evaluated for signs and/or symptoms of depression at each visit using the [PHQ-9](#).

The treatment of IFN-induced depression includes the use of antidepressants, particularly selective serotonin reuptake inhibitors (SSRIs). Unlike in other depressive states where depressive symptoms may not abate for 4-6 weeks after initiating therapy, in IFN-induced depression response may occur as quickly as 2 weeks and is 80% effective.

ii. Duration of Antidepressant Therapy

In all patients with treatment-emergent depression, antidepressants should be continued for the total duration of HCV treatment and for 2 to 3 months after treatment cessation.

Early discontinuation of antidepressant therapy without an adequate “washout” period after HCV treatment discontinuation is frequently associated with a rebound in depressive symptoms.

F. Management of Anemia

Anemia in HCV treatment is predominantly due to ribavirin’s accumulation within the red blood cell (RBC) and subsequent oxidative membrane damage causing hemolysis. Declines of >3 g/dL affect the majority of patients treated with ribavirin and PEG-IFN. Although PEG-IFN can also cause anemia, the extent of anemia is far lower than with ribavirin and due mostly to bone marrow suppression.³⁸ **Anemia is expected to be minimal with the use of sofosbuvir and simeprevir.**

Ribavirin exposure was previously shown to affect initial response, SVR, and relapse rates for patients with genotype 1 or 4 infection.³⁹ Historically, the pharmacological management of anemia involved the use of erythropoiesis stimulating agents (ESA) including erythropoietin and darbepoietin. It is likely that ribavirin-induced anemia was exacerbated by the concomitant use of interferon. **Neither sofosbuvir nor simeprevir is expected to exacerbate anemia, however data are limited to clinical trials.** For patients experiencing anemia, the initial recommendation is for ribavirin dose reduction. If the anemia cannot be managed with dose reduction alone, ESAs can be used on a case by case basis in consultation with ECHO® experts.

For patients requiring ESAs to manage anemia, erythropoietin is dosed at 40,000-60,000 units SQ weekly.⁴⁰ Response can occur as early as 2 weeks after starting therapy, with a median improvement of

hemoglobin to 11-13 g/dL in 35 days. Patients should have their dose of erythropoietin increased if the change in hemoglobin is less than 1 g/dL after 2 weeks of treatment.⁴¹ Additionally, patients failing to respond should be evaluated for iron deficiency and any underlying vitamin deficiency including folic acid or vitamin B12. Increasing the frequency of dosing from once weekly to three times weekly was not found to be effective in faster hemoglobin response or greater improvements in patient QOL.^{42,43}

Darbepoietin-alfa is an analogue of recombinant epoetin with a longer half-life than erythropoietin resulting in slower clearance and greater in vivo activity thereby requiring less frequent dosing than erythropoietin. Darbepoietin in HCV treatment has been studied at a dose 3 mcg/kg SQ every 2 weeks, resulting in statistically significant improvements in hemoglobin increase after 81 days and improved patient quality of life. Alternatively, a dose of 200 micrograms of darbepoietin every 2 weeks is equivalent to an epoetin dose range of 32,000-89,999 units weekly. Moreover, patients experiencing resistance to epoetin may respond to darbepoietin.⁴⁴ The main limitation of darbepoietin-alfa is a longer onset of action with a median improvement of hemoglobin to 11-13 g/dL in 81 days compared to 35 days for epoetin alfa.

The FDA issued a black box warning for ESAs due to increased mortality from serious cardiovascular and thromboembolic events as well as a potential for tumor progression. A retrospective study of ESAs specifically in HCV treatment found no increased risk of thromboembolic events or increase in development of HCC. Nonetheless, patients on HCV treatment requiring the use of ESAs should have a target hemoglobin level of 10-12 g/dL.⁴⁵ ESAs are not FDA approved for use in HCV treatment associated anemia.

Recommendations:

1. The decision to reduce ribavirin should be based on individual patient characteristics and response of the hemoglobin level to ribavirin. Variables that affect this decision are baseline hemoglobin, renal function, slope of the hemoglobin decline during the first 2-4 weeks of treatment, age, medical comorbidities, altitude, and presence or absence of cirrhosis.
2. Consider reducing ribavirin in patients who experience $\geq 25\%$ decline in hemoglobin within a 4 week period.
3. Do not dose reduce sofosbuvir or simeprevir to manage anemia.
4. For Hgb < 10 g/dl repeat CBC, contact ECHO[®] HCV specialist or present to HCV Clinic within 72 hours. If < 8.5 g/dl hold RBV and contact ECHO[®] HCV specialist immediately. Patients with a hemoglobin <10 g/dL due to ribavirin may require the use of erythropoietin stimulating agents.
5. The initial erythropoietin dose is 40,000 units SQ weekly. The dose may be increased to 60,000 units weekly if there is a less than 1 g/dL response in hemoglobin after 2 weeks of therapy. Alternatively, darbepoietin may be used at a dose of 200 micrograms SQ every 2 weeks.

G. Management of Neutropenia

Interferon induced neutropenia is an established laboratory abnormality more common with PEG-IFN than with traditional interferon. Risk factors for increased risk of developing infection included presence of cirrhosis or severe fibrosis.⁴⁶

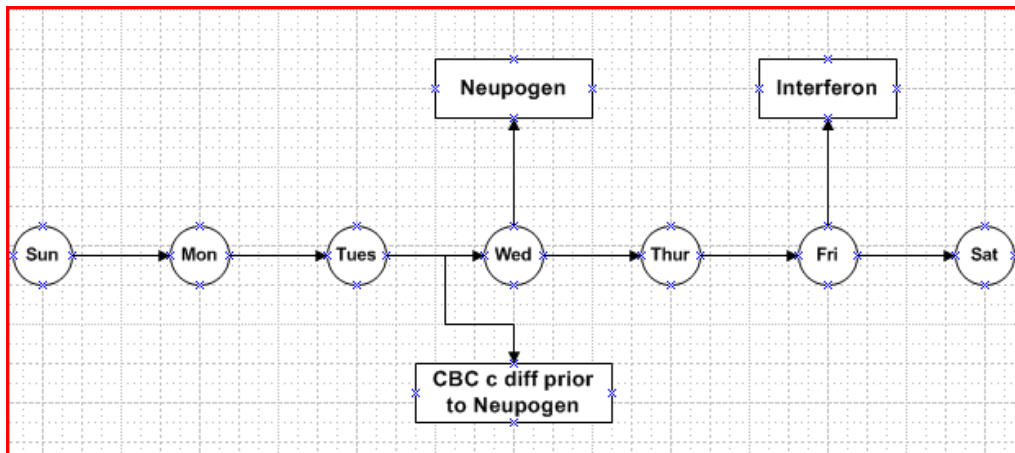
Although the manufacturers of PEG-IFN have established absolute neutrophil count (ANC) criteria for dose reductions at an ANC <750 mm³ and therapy discontinuation at an ANC of <500 mm³, in cancer chemotherapy guidelines neutropenia is defined as <500 mm³ with the greatest risk for bloodstream infections when the ANC <100 mm³. There are no studies specifically in the HCV patient population suggesting interferon induced neutropenia is more severe than among patients undergoing cancer chemotherapy. Furthermore, a small study of HCV patients during treatment suggests an increase in innate immune function during exposure to peg-IFN and ribavirin which may counteract the reduced ANC.⁴⁷

The use of granulocyte colony stimulating factors (G-CSF) on SVR has been evaluated in a small group of patients and may be associated with achievement of SVR.⁴⁸ The use of G-CSF increases neutrophil counts and is an effective means of preventing PEG-IFN dose reductions or premature treatment discontinuation. G-CSF is not FDA approved for IFN induced neutropenia, however it has been used widely in clinical practice. The optimal timing of G-CSF in HCV treatment is prior to interferon injections. One study documented an average increase of 3100 cells/μL when G-CSF was given 2 days prior to IFN injection compared to an increase of 2000 cell/μL if given after IFN injection.⁴⁹ Increase in ANC may be observed within 12 hours of injection and last approximately 4 days.

Recommendations:

1. Interferon induced neutropenia should not be managed by dose reductions or treatment termination unless clinical signs or symptoms of infection and discussion with ECHO® medical specialist. For ANC < 500, present to HCV clinic within 72 hours or call ECHO® HCV specialist for recommendation. Do not give another dose of IFN until you have talked to an ECHO® HCV specialist. Anticipate the start of Neupogen® 300 mcg/sc/wk.
2. If G-CSF started, monitor CBC with differential after 1 week and every 2 weeks thereafter.
3. G-CSF should be injected 2 days prior to PEG-IFN injections. Patients failing to demonstrate adequate increases in ANC may consider twice weekly injections of G-CSF.
4. In general, ANC should be checked immediately prior to PEG-IFN injections. However, patients on G-CSF should have the ANC checked immediately prior to the G-CSF injection.

Figure 1: Neupogen Dosing and Lab Monitoring



H. Management of Thrombocytopenia

For platelet count < 25,000/ul, hold IFN, present to the HCV TeleECHO clinic within 72 hours or call ECHO® HCV specialist for recommendation. Eltrombopag, an oral thrombopoetin receptor agonist, is currently approved for use in the management of HCV to minimize the need for PegIFN dose reductions. The studies of eltrombopag in HCV were not performed in combination with PI or sofosbuvir-based therapies and the role of this agent is not well defined.

I. Treatment Stopping Rules

Stopping rules currently exist only for simeprevir with pegylated interferon/riba.

Table 8: Treatment Stopping Rules for Simeprevir Based Therapy

HCV RNA	Action
Treatment week 4: Greater than or equal to 25 IU/mL	Stop simeprevir, PEG-IFN, and ribavirin
Treatment week 12: Greater than or equal to 25 IU/mL	Stop simeprevir, PEG-IFN, and ribavirin
Treatment week 24: Greater than or equal to 25 IU/mL	Stop PEG-IFN and ribavirin

J. Patient Safety Summary

In order to ensure increased patient safety during treatment, closer monitoring is required for some patients. Treating sites are responsible for reviewing all laboratory results and PHQ-9 scores. If treatment results in any of the following conditions the patient will likely require more frequent monitoring:

- PHQ-9 score ≥ 15
- Decline in Hgb more than 1 g/dl per week
- Hgb to < 11 g/dl
- ANC < $1.0 \times 10^9/L$
- Platelets < $50.0 \times 10^9/L$

K. Post Treatment

Patients with undetectable HCV RNA at the end-of-treatment (ETR) should have an HCV RNA done 12 weeks after completing therapy. Long-term follow-up studies indicate that SVR represents durable eradication (cure) of HCV infection. If HCV RNA is detected following an end of treatment response, the patient has experienced virologic relapse and no additional HCV RNA monitoring is indicated.

GUIDELINES FOR PRESENTATION TO ECHO® CLINIC

A. Reasons to Present a Patient

1. Initial presentation for work up for treatment.
2. Patient previously presented with recommendations for further work-up.

Patients on treatment should be presented for the following reasons:

- Report viral load results (any time during treatment)
- End of treatment viral load and labs
- 12 week post treatment viral load and labs
- For assistance in managing any side effects or laboratory abnormalities
- Hemoglobin < 11 g/dl, has dropped ≥ 4 g from starting value, or has dropped ≥ 2 g since last lab draw
- Patient on ESA to manage anemia and Hgb > 11.5 g/dl
- ANC < 500
- Platelet count < 25,000

B. Downloadable forms

- i. [2014 CME Credit Sign In Sheet](#)
- ii. [2014 CME Evaluation Form](#)
- iii. [HCV Initial Presentation Form](#)
- iv. [HCV Follow-up Presentation Form](#)

C. How to Submit a Patient Case:

- i. Submitting patient cases via [iHealth](#)

iHealth is a web-based disease management tool that was specifically designed to help providers manage and present patients being treated for HCV. iHealth will take a patient's screening data, start of treatment data, and lab work and create a convenient summary of the patient's progress through treatment.

Through iHealth, a provider can schedule a presentation for a patient. Scheduling through iHealth replaces the need to fax the paper presentation forms.

For video instructions on How to Use iHealth, please click on the following link: [Video Quick Start Guide](#).

iHealth will gather the relevant encounter data or lab work for the patient, allowing the clinic coordinator to show all attendees a de-identified presentation forms for the patient.

The screenshot shows a web browser window displaying a patient's protocol summary. The page has a navigation bar with 'My Messages', 'Patients', 'Admin', 'Reports', 'Resources', and 'Presentation System'. Below this is a search bar and a 'Patient Details' section with fields for Site, Name, Age, ECHO ID, Date of Birth, Start Date, HCV Genotype, and Current Week. A 'Current Medications' section lists several drugs. The main part of the page is a table with tabs for 'Messages', 'Protocol', 'Clinical', 'Encounters', 'Lab', 'Flow Sheet', 'Medications', 'Reports', and 'Presentation'. The 'Lab' tab is active, showing a grid of lab results for various tests (WBC, ANC, HGB, HCT, Platelets, Creatinine, AST SGOT, ALT SGPT, Total Prot, Albumin, T. Bill, Dir Bill, Alk Phos, Uric Acid, Triglycerides, TSH, HCV-VL IU/ml, CESD) across 48 weeks. The 'Actual Date' column shows dates for each week, and the 'Due Date' column shows dates for each week. The table is partially filled with numerical values.

Project ECHO® is currently making the transition to paperless presentations through iHealth. A Project ECHO® staff member will arrange a time to conduct iHealth training for interested staff at your site.

ii. If iHealth is unavailable?

Patient cases may be faxed using one of two paper presentation forms, initial or follow up. Use the initial presentation sheet for first time patient cases. Thereafter, all presentations should be made using the follow up presentation sheet.

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