Treatment of Hepatitis C Guideline

These clinical guidelines are designed to assist clinicians by providing an analytical framework for the evaluation and treatment of patients. They are not intended to replace a clinician’s judgment or to establish a protocol for all patients with a particular condition. A guideline will rarely establish the only approach to a problem.

**GUIDELINE HISTORY and APPROVAL**

<table>
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<tr>
<th>ACTION</th>
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                            | Sept. 4, - Dec 30, 2007  
                            | Geisinger Health Plan Clinical Guideline Committee |
| Guideline reviewed         | Same as above                                                                                                           | 4/23/08                | Gesinger Health Plan Quality Improvement Committee |
                            | http://www.aasld.org/practiceguidelines/Pages/NewUpdatedGuidelines.aspx  
                            | Dec. 21, 2009 – April 1, 2010  
                            | Geisinger Health Plan Clinical Guideline Committee |
| Guideline reviewed         | Same as above                                                                                                           | 4/28/10                | Gesinger Health Plan Quality Improvement Committee |
                                    | http://www.hcvguidelines.org/full-report-view  
                                    | 2/1/14- 4/15/14          | Geisinger Health Plan Clinical Guideline Committee |
| Guideline reviewed         | Same as above                                                                                                           | 4/30/14                | Gesinger Health Plan Quality Improvement Committee |
OVERVIEW
Hepatitis C is a blood-borne, infectious, viral disease that is caused by a hepatotropic virus called Hepatitis C virus (HCV). The infection can cause liver inflammation (hepatitis) that is often asymptomatic, but ensuing chronic hepatitis can result later in cirrhosis (fibrotic scarring of the liver) and liver cancer.

The hepatitis C virus (HCV) is spread by blood-to-blood contact with an infected person’s blood. The symptoms can be medically managed, and a proportion of patients can be cleared of the virus by a course of anti-viral medicines. Although early medical intervention is helpful, people with HCV infection often experience mild symptoms, and consequently do not seek treatment. Approximately 1.6% of the U.S. population is positive for anti-HCV antibody, and 1.3% is chronically infected with HCV. In the U.S., those with a history of intravenous drug use, inhaled drug usage, tattoos, or who have been exposed to blood via unsafe sex or social practices are increased risk for this disease. Hepatitis C is the leading cause of liver transplant in the United States.

SEED GUIDELINE(S)
American Association for the Study of Liver Disease (AASLD) Practice Guideline.
Recommendations for testing, managing and Treating Hepatitis C. 2014
http://www.aasld.org/practiceguidelines/Pages/NewUpdatedGuidelines.aspx

Provisional Guidance on the Use of Hepatitis C Virus Protease Inhibitors for Treatment of Hepatitis C in HIV-Infected Persons. HIV/AIDS. CID 2012:54 April

GOALS
Promote the standardization and availability of diagnostic tests for HCV infection and its complications, leading to early diagnosis and the implementation of appropriate treatment practices and ensuring adherence for potential cure.

FAST FACTS
- Hepatitis C is the leading cause of liver transplant in the United States.
- An estimated 4 million people in the United States are infected with hepatitis C.
- Fifty-five to 85 percent of people infected with HCV develop chronic infection and 75 percent of those with chronic infection develop chronic liver disease.
Several serological tests are now available and used for screening, diagnosis, and monitoring treatment including Enzyme Immunoassay, Recombinant Immunoblot Assay, Polymerase Chain Reaction (PCR) Amplification, and Genotyping and Serotyping.

HCV infection is asymptomatic or paucisymptomatic in 90% of cases.

RECOMMENDATIONS FOR SCREENING

Persons for Whom HCV testing is Recommended

- All persons who were born between 1945 and 1965
- Persons who have injected illicit drugs in the recent and remote past, including those who injected only once and do not consider themselves to be drug users
- Persons with conditions associated with a high prevalence of HCV infection, including:
  - Persons with HIV infection
  - Persons with hemophilia who received clotting factor concentrates before 1987
  - Persons who were ever on hemodialysis
  - Persons with unexplained abnormal aminotransferase levels
- Prior recipients of transfusions or organ transplants, including:
  - Persons who were notified that they had received blood from a donor who later tested positive for HCV infection
  - Persons who received a transfusion of blood or blood products before July 1992
  - Persons who received an organ transplant before July 1992
- Children born to HCV-infected mothers
- Health care, emergency medical and public safety workers after a needle stick injury or mucosal exposure to HCV-positive blood
- Current sexual partners of HCV-infected persons
- Persons with non-professional tattoos, history of nasal cocaine inhalation or unexplained liver function abnormalities.

ABBREVIATIONS

HCV – hepatitis C virus  EIA – enzyme immunoassay
EVR – early virologic response  RVR – rapid viral response
SVR – sustained viral response  PCR – polymerase chain reaction
Qualitative PCR – detects whether the hepatitis C virus is present or not
Quantitative PCR – estimates the number of HCV virus per ml of blood
PCR genotype – looks for the virus and determines the particular subtype of HCV
SCREENING FOR HCV INFECTION ALGORITHM
Adapted from Centers for Disease Control and Prevention (CDC), 2013. (Centers for Disease Control and Prevention [CDC], 2013)
HCV SCREENING

- Persons recommended for screening should be tested for HCV antibodies (anti-HCV) using an FDA approved test via laboratory assays or point of service assays such as OraQuick HCV Rapid Antibody Test
- HCV RNA testing should be performed in
  (a) patients with a positive anti-HCV test
  a. Patients who test positive for antibodies without HCV RNA present should be presumed to have no active infection
  (b) patients for whom antiviral treatment is being considered, using a quantitative assay to determine the baseline level of viremia
  (c) patients with unexplained liver disease whose anti-HCV test is negative and who are immunocompromised or suspected of having acute HCV infection
- HCV genotype should be determined in all HCV-infected persons prior to treatment in order to determine an appropriate therapy and duration of treatment

REDUCING DISEASE PROGRESSION AND TRANSMISSION

- All identified HCV positive patients should be instructed on preventing transmission to others by avoiding blood exposure to others
- Consumption of alcohol can accelerate liver damage in patients with HCV therefore abstinence from alcohol is critical in reducing liver disease progression prior to, during and following treatment
- Identification of other infectious diseases such as HIV/AIDS or HBV and managed
- Patients with metabolic syndrome or a body mass index \( \geq 25 \) kg/m\(^2\) should be counseled in weight reduction

TREATMENT

Treatment regimens are evolving and new agents are currently being evaluated and brought to market. It is advisable to consult the latest version of the AASLD guidelines and to consider referral to a Hepatitis C treatment center of excellence as defined by Geisinger health Plan’s Credentials Committee.

Note: Pharmaceutical coverage is dependent upon individual pharmacy benefit design and certain drugs may require prior authorization. Providers are encouraged to review the GHP formulary at http://www.thehealthplan.com, or contact the GHP Pharmacy Department at 1-800-988-4861.

Characteristics of Persons for Whom Therapy is Accepted

- At least 18 years of age
- Positive polymerase chain reaction (PCR) testing
- Liver biopsy showing chronic hepatitis with significant fibrosis (more-than-portal fibrosis: Metavir score \( \geq 2 \); Ishak score \( \geq 3 \)) - optional
• Model for End-Sage Liver Disease (MELD) score ≤ 15 (Calculated using serum creatinin, bilirubin and INR values. Calculator can be found at http://www.unos.org/resources/MeldPeldCalculator.asp?index=98)
• Acceptable hematological and biochemical indices (hemoglobin > 13 g/dL for men and >12 g/dL for women; neutrophil count > 1.5 k/mm3; creatinine <1.5 mg/dL)
• No history of depression or the condition is well controlled and patient is cleared after psych evaluation.
• Willing to be treated and to conform to treatment requirements

**Characteristics of Persons for Whom Therapy Should Be Individualized**

- Failed prior treatment (nonresponders and relapsers) consisting of either interferon given alone or in combination with ribavirin, or consisting of peginterferon given alone
- Current users of illicit drugs or alcohol but willing to participate in a substance abuse program (such as a suboxone program) or alcohol support program
- Liver biopsy evidence of either no or only mild fibrosis (portal fibrosis: Metavir score < 2; Ishak score < 3)
- Acute hepatitis C
- Coinfected with HIV
- Under 18 years of age
- Chronic renal disease (on or not on hemodialysis)
- Decompensated cirrhosis
- Liver transplantation recipient

**Contraindications to HCV Therapy**

- Major, uncontrolled depressive illness
- Ongoing injection drug use* or illegal drug use
- Ongoing alcohol abuse
- Untreated thyroid disease
- Uncontrolled autoimmune disorders
- Pregnant or unwilling/unable to comply with adequate contraception
- Life-determining extrahepatic disease (malignancy, unstable angina, severe COPD)
- Known hypersensitivity to drugs used to treat HCV

* Unless the patient is on a methadone maintenance program, and provided they wish to take HCV treatment and are able and willing to maintain close monitoring and practice contraception.

**TREATMENT ALGORITHMS**

**Treatment of Genotype-1 HCV Infection**

Patients who are Treatment-Naïve:
• Daily sofosbuvir (400 mg) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [>75 kg]) plus weekly PEG for 12 weeks is recommended for IFN-eligible persons with HCV genotype 1 infection, regardless of subtype.

• Daily sofosbuvir (400 mg) plus simeprevir (150 mg), with or without weight-based RBV (1000 mg [<75 kg] to 1200 mg [>75 kg]) for 12 weeks is recommended for IFN-ineligible patients with HCV genotype 1 infection, regardless of subtype.

IFN ineligible is defined as one or more of the below:
  • Intolerance to IFN
  • Autoimmune hepatitis and other autoimmune disorders
  • Hypersensitivity to PEG or any of its components
  • Decompensated hepatic disease
  • Major uncontrolled depressive illness
  • A baseline neutrophil count below 1500/μL, a baseline platelet count below 90,000/μL or baseline hemoglobin below 10 g/dL
  • A history of preexisting cardiac disease patients with HCV genotype 1 infection, regardless of subtype.

• Daily simeprevir (150 mg) for 12 weeks and weight-based RBV (1000 mg [<75 kg] to 1200 mg [>75 kg]) plus weekly PEG for 24 weeks is an acceptable regimen for IFN-eligible persons with either:
  1. HCV genotype 1b or
  2. HCV genotype 1a infection in whom the Q80K polymorphism is not detected prior to treatment

• Daily sofosbuvir (400 mg) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [>75 kg]) for 24 weeks is an acceptable regimen for IFN-ineligible persons with HCV genotype 1 infection, regardless of subtype; however, preliminary data suggest that this regimen may be less effective than daily sofosbuvir (400 mg) plus simeprevir (150 mg), particularly among patients with cirrhosis.

Treatment of Genotype-2 HCV Infection

• Daily sofosbuvir (400 mg) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [>75 kg]) for 12 weeks is recommended for treatment-naive patients with HCV genotype 2 infection.

Treatment of Genotype-3 HCV Infection

• Daily sofosbuvir (400 mg) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [>75 kg]) for 24 weeks is recommended for treatment-naive patients with HCV genotype 3 infection.
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- Daily sofosbuvir (400 mg) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [>75 kg]) plus weekly PEG for 12 weeks is an acceptable regimen for IFN-eligible persons with HCV genotype 3.

Treatment of Genotype-4 HCV Infection

- Daily sofosbuvir (400 mg) plus weight-based RBV (1000 mg [<75 kg] to 1200 mg [>75 kg]) for 24 weeks is recommended for IFN-ineligible patients with HCV genotype 4 infection.

- Daily simeprevir (150 mg) for 12 weeks and weight-based RBV (1000 mg [<75 kg] to 1200 mg [>75 kg]) plus weekly PEG for 24 to 48 weeks is an alternative regimen for IFN-eligible persons with HCV genotype 4 infection.

Treatment of Genotype-5 or 6 HCV Infection

- Daily sofosbuvir (400 mg) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [>75 kg]) plus weekly PEG for 12 weeks is recommended for IFN-eligible persons with HCV genotype 5 or 6 infection.

- Daily weight-based RBV (1000 mg [<75 kg] to 1200 mg [>75 kg]) plus weekly PEG for 48 weeks is an acceptable regimen for persons infected with HCV genotype 5 or 6.

RETREATMENT in Genotype 1

Recommended regimen for HCV genotype 1 PEG/RBV (without an HCV protease inhibitor) nonresponder patients:

- Daily sofosbuvir (400 mg) plus simeprevir (150 mg), with or without weight-based RBV (1000 mg [<75 kg] to 1200 mg [>75 kg]) for 12 weeks is recommended for retreatment of HCV genotype 1 infection, regardless of subtype or IFN eligibility.

Recommended regimen for HCV genotype 1 PEG/RBV (with an HCV protease inhibitor) nonresponder patients:

- Daily sofosbuvir (400 mg) for 12 weeks plus weight-based RBV (1000 mg [<75 kg] to 1200 mg [>75 kg]) and weekly PEG for 12 to 24 weeks is recommended for retreatment of HCV genotype 1 infection, regardless of subtype.

Alternative regimen for PEG/RBV (with or without an HCV protease inhibitor) nonresponder patients with HCV genotype 1.

- Daily sofosbuvir (400 mg) for 12 weeks and weight-based RBV (1000 mg [<75 kg] to 1200 mg [>75 kg]) plus weekly PEG for 12 to 24 weeks is an alternative for retreatment of IFN-eligible persons with HCV genotype 1 infection, regardless of subtype.
- Daily sofosbuvir (400 mg) for 24 weeks and weight-based RBV (1000 mg [<75 kg] to 1200 mg [>75 kg]) for 24 weeks is an alternative for retreatment of IFN-ineligible persons with HCV genotype 1 infection, regardless of subtype.

Alternative regimen for PEG/RBV (without an HCV protease inhibitor) nonresponder patients with HCV genotype 1 who are eligible to receive IFN.

- Daily simeprevir (150 mg) for 12 weeks plus weight-based RBV (1000 mg [<75 kg] to 1200 mg [>75 kg]) and weekly PEG for 48 weeks is an alternative for IFN-eligible persons with HCV genotype 1 infection. (All patients with cirrhosis who are receiving simeprevir should have well compensated liver disease.)

**RETREATMENT in Genotype 2**

Recommended regimen for genotype 2 PEG/RBV nonresponders.

- Daily sofosbuvir (400 mg) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [>75 kg]) for 12 weeks is recommended for retreatment of HCV genotype 2 infection. (Patients with cirrhosis may benefit by extension of treatment to 16 weeks.)

Alternative regimen for PEG/RBV nonresponder patients with HCV genotype 2 infection who are eligible to receive IFN.

- Retreatment with daily sofosbuvir (400 mg) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [>75 kg]) plus weekly PEG for 12 weeks is an alternative for IFN-eligible persons with HCV genotype 2 infection.

**Persons With HIV Coinfection**

Pending more conclusive data and regulatory approval, decisions to use or withhold HCV PIs in HIV/HCV-coinfected persons must take into account multiple related factors.

- liver fibrosis progression is more rapid and peginterferon and ribavirin treatment is less effective in HIV/ HCV-coinfected persons than in those without HIV
- liver transplantation is neither widely available nor highly successful in HIV/HCV-coinfected persons
- the safety and efficacy of HCV PIs are largely unproven in HIV/ HCV-coinfected persons, data regarding drug-drug interactions are limited, additional anti-HCV medications are being developed, and the price of HCV PIs may add to the cost of the peginterferon and ribavirin treatment regimen.

General Guidance

- Anti-HCV testing should be performed in all HIV-infected persons.
- HCV RNA testing should be performed to confirm HCV infection in HIV-infected persons who are positive for anti-HCV, as well as in those who are negative and have evidence of unexplained liver disease.
- Hepatitis C should be treated in the HIV/HCV-coinfected person in whom the likelihood of serious liver disease and a treatment response are judged to outweigh the risk of morbidity from the adverse effects of therapy.
- Initial treatment of hepatitis C in most HIV infected persons is peginterferon alfa plus ribavirin for 48 weeks.
- Given the high likelihood of adverse events, HIV/HCV-coinfected patients on HCV treatment should be monitored closely.
- Ribavirin should be used with caution in persons with limited myeloid reserves and in those taking zidovudine and stavudine. When possible, patients receiving ddI should be switched to an equivalent antiretroviral before beginning therapy with ribavirin.
- HIV-infected patients with decompensated liver disease should not be treated with peginterferon alfa and ribavirin and may be candidates for orthotopic liver transplantation.

Persons With Renal Disease

- All persons with chronic kidney disease awaiting hemodialysis or transplant should be screened for hepatitis C in order to plan for management and treatment
- The decision to perform a liver biopsy in patients with renal disease should be individualized based on the clinical assessment of the need for therapy and the need to establish the severity of liver disease.
- Eligible patients with renal insufficiency or end-stage renal disease and HCV may be treated with interferon.
- Persons with chronic HCV infection and severe kidney disease not undergoing hemodialysis can be treated with reduced doses of both peginterferon (alpha-2a, 135µg/week; alpha-2b, 1 µg/kg/week) and ribavirin (200-800 mg/day) with careful monitoring for adverse effects.
- Treatment of HCV in patients on dialysis may be considered with either standard interferon (2a or 2b) in a dose of 3 mU t.i.w. or reduced dose pegylated interferon 2a, 135µg/week or 2b 1 µg/kg/week. Ribavirin can be used in combination with interferon in a markedly reduced daily dose with careful monitoring for anemia and other adverse effects.
- Treatment is not recommended for patients with chronic HCV infection who have undergone kidney transplantation, unless they develop fibrosing cholestatic hepatitis.
- Patients with cryoglobulinemia and mild to moderate proteinuria and slowly progressive kidney disease can be treated with either standard interferon or reduced doses of pegylated interferon alfa and ribavirin.
- Patients with cryoglobulinemia and marked proteinuria with evidence of progressive kidney disease or an acute flare of cryoglobulinemia can be treated with rituximab,
cyclophosphamide plus methylprednisolone, or plasma exchange followed by interferon-based treatment once the acute process has subsided.

- Patients with renal failure should not be treated with ribavirin.

**Persons With Decompensated Cirrhosis**


- Patients with clinically decompensated cirrhosis should be referred for consideration of liver transplantation.
- Antiviral therapy may be initiated at a low dose in patients with mild degrees of hepatic compromise, as long as treatment is administered by experienced clinicians, with vigilant monitoring for adverse events, preferably in patients who have already been accepted as candidates for liver transplantation.
- Growth factors can be used for treatment-associated anemia (epoetin) and leukopenia (G-CSF, GM-CSF) and may limit the need for antiviral dose reductions in patients with decompensated cirrhosis.

**Treatment After Solid Organ Transplant**

- Treatment of HCV-related disease following liver transplantation should be undertaken with caution because of the increased risk of adverse events and should be performed under the supervision of a physician experienced in transplantation.
- Peginterferon alfa either with or without ribavirin should be the preferred regimen when treating patients with hepatitis C after liver transplantation.
- Antiviral therapy is generally contraindicated in recipients of heart, lung, and kidney grafts.

**Persons With Acute Hepatitis C**

- The diagnosis of acute hepatitis C in patients with new-onset, unexplained liver disease should be confirmed by measuring HCV RNA in serum.
- Although excellent results were achieved in reported uncontrolled studies using standard interferon monotherapy, it is appropriate to consider the use of peginterferon because of its improved ease of administration.
- No recommendation can be made about the addition of ribavirin, and the decision will therefore need to be considered on a case-by-case basis.
- In the absence of controlled study data, no definitive recommendations can be made about the timing of treatment initiation; however, it seems reasonable to delay treatment for 2 to 4 months after acute onset to allow for spontaneous resolution.
- No definitive recommendation can be made about the duration of treatment needed to treat acute hepatitis C; however, it seems reasonable to continue treatment for at least 6 months.

**Persons Actively Using Illicit Injection Drugs**
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- Treatment of HCV infection should not be withheld from persons who currently use illicit drugs or who are on a methadone maintenance program, provided they wish to take HCV treatment and are able and willing to maintain close monitoring and practice contraception.
- The decision of whether to treat should be made considering the anticipated risks and benefits for the individual.
- Continued support from drug abuse and psychiatric counseling services is an important adjunct to treatment of HCV infection in persons who use illicit drugs.

REFERENCES


Yee HS, Currie SL, Darling JM, Wright TL. Management and treatment of hepatitis C viral infection: Recommendations from the Department of Veterans Affairs Hepatitis C Resource Center Program and the National Hepatitis C Program office. Am J Gastroenterol 2006; 101:2360-2378.


Tucker ME. Hepatitis C viral suppression reduces Liver morbidity, death. Medscape Medical News [serial online]. November 15, 2013


A SPECIAL MEETING REVIEW EDITION: Advances in the Treatment of Hepatitis C Virus Infection From EASL 2013: The 48th Annual Meeting of the European Association for the Study of the LiverApril 24-28, 2013 • Amsterdam, The NetherlandsSpecial Reporting on:• Simeprevir Plus Peginterferon/Ribavirin Is Associated with a High SVR12 Rate in Treatment-Naive Patients with Genotype 1 Hepatitis C Virus Infection• Addition of Simeprevir to Peginterferon/Ribavirin Is Associated with Faster Resolution of Fatigue in Treatment-Naive Patients• Sofosbuvir Plus Ribavirin Demonstrates Significant Efficacy in Multiple HCV Genotype 2/3 Populations• Daclatasvir Plus Sofosbuvir with or without Ribavirin Yields 100% SVR24 Rate in Genotype 1 Patients Who Fail Telaprevir or Boceprevir• Addition of TG4040 Vaccine to Peginterferon/Ribavirin Increases Sustained Virologic Response Rate at 24 Weeks in Genotype 1 Hepatitis C InfectionPLUS Meeting Abstract Summaries With Expert Commentary by: Ira M. Jacobson, MDJoan Sanford I. Weill Medical College at Cornell UniversityNew York, New York. Gastroenterol Hepatol (N Y). Jun 2013;9(6 Suppl 3):1-18