

American Gastroenterological Association Medical Position Statement on the Management of Hepatitis C

Hepatitis C accounts for a sizable proportion of cases of chronic liver disease, liver disease deaths, and cases of hepatocellular carcinoma and represents the most common indication for liver transplantation. Projections based on the current prevalence of infection and anticipated rates of progression suggest that the morbidity and mortality, as well as the medical care costs attributable to hepatitis C virus (HCV) infection, will escalate alarmingly during the next 2 decades.

The substantial clinical and economic impact of hepatitis C focuses attention on the critical need to prevent and control HCV infection. Public health measures, changes in behavior to avoid blood-borne infections, and screening of donated blood and organs for HCV have reduced dramatically the frequency of new infections, and substantial progress has been achieved in antiviral therapy for hepatitis C. Applied effectively, contemporary antiviral therapy can prevent chronic infection in almost all persons with acute hepatitis C and can cure chronic liver disease associated with HCV infection in as many as half of patients with compensated, HCV-associated liver disease. In short, hepatitis C is an important public health problem whose consequences can be reduced by appropriate application of antiviral therapy. Because the demand for management of chronic hepatitis C has increased so considerably over the past decade, the American Gastroenterological Association developed a technical review¹ and this medical position statement.

This medical position statement, which contains practice guidelines intended for physicians, nurse practitioners, physician assistants, and other health care workers who participate in the care of patients with hepatitis C, includes suggestions for preferable approaches to the management of persons with hepatitis C. These guidelines, which are recommendations intended to assist physicians and other health care workers in arriving at reasoned patient care decisions,² are designed to be flexible rather than rigidly inflexible universally applied "standards of care." Although these recommendations should be followed in most cases, management decisions are left to the individual physician and health care worker based on the circumstances of the individual patient. As in previous guidelines issued by the American Gastroenterological As-

sociation, specific recommendations are based on relevant published information.

Screening

Routine screening of all asymptomatic adults, who have a low prior probability of HCV infection, is not recommended. Among high-risk groups (eg, injection drug users, persons who received a transfusion before 1992 [when donor screening for antibody to HCV was introduced], persons with hemophilia who received clotting factors before 1987, persons with frequent percutaneous exposures, immigrants from countries with a high prevalence of HCV infection, and persons with clinical or biochemical evidence for chronic liver disease, even among asymptomatic persons), diagnostic testing for HCV infection has been recommended by the US Public Health Service, expert panels, and professional medical specialty societies. Spouses of persons with chronic hepatitis C are also candidates for HCV serologic testing. Persons in whom the diagnosis of hepatitis C is established are candidates for hepatitis A and hepatitis B vaccines.

Pretreatment Diagnostic Evaluation of Patients With Chronic Hepatitis C

Persons with a reactive enzyme immunoassay for antibody to HCV, the presence of HCV RNA, and compensated liver disease are potential candidates for antiviral therapy. Currently, antiviral therapy is not recommended routinely for patients with hepatic decompensation; patients with a history of severe, uncontrolled psychiatric disorder; and/or patients with severe hematologic cytopenias.

Elevation of alanine aminotransferase (ALT) and aspartate aminotransferase levels is not a requirement for therapy. All candidates for antiviral therapy should be tested for HCV RNA with a quantitative amplification assay and should be tested for HCV genotype.

Patients in whom antiviral therapy is being considered are candidates for liver biopsy, the gold standard for

determining histologic grade and stage, unless the potential for complications is unacceptably high. For patients with moderate to severe fibrosis (Ishak stage ≥ 3 , METAVIR stage $\geq F2$; please see technical review¹ for histologic scoring systems), antiviral therapy is recommended uniformly. For patients with milder histologic disease, progression may be sufficiently slow to justify monitoring without imminent therapeutic intervention in a proportion of these patients (see Treatment Recommendations). For patients with genotypes 2 and 3, the likelihood of response is so high that the benefits of treatment may outweigh the importance of histologic considerations; therefore, some authorities forego a baseline liver biopsy in patients with genotypes 2 and 3. Data to support routine ultrasonography for localization of the liver before liver biopsy are insufficient to justify mandating prebiopsy ultrasonography in all cases and for all practitioners regardless of levels of skill and experience.

Treatment of Chronic Hepatitis C

The current standard of care for the treatment of previously untreated patients with chronic hepatitis C is combination pegylated interferon (PEG-IFN) alfa by subcutaneous injection once a week and oral ribavirin daily. For patients with contraindications to ribavirin but who have indications for antiviral therapy, PEG-IFN represents the best available treatment.

Two PEG-IFN alfa preparations are available: (1) PEG-IFN alfa-2b, administered at a weight-based, 1.5- μ g/kg dose, and (2) PEG IFN alfa-2a, administered at a fixed, 180- μ g dose. Randomized controlled trials (RCTs) have shown that combination PEG-IFN alfa and ribavirin therapy can achieve a sustained virologic response (SVR) in 54%–56% of patients: 42%–52% of patients with genotype 1 and 76%–84% of those with genotypes 2 and 3. Whether one of these PEG-IFN/ribavirin regimens or weight-based modifications of the 2 regimens will prove to be superior is the subject of ongoing trials. Predictors of response to therapy in these large RCTs are displayed in Table 1.

The results of a single, large RCT support a recommendation that patients with genotype 1 require 48 weeks of therapy with higher daily doses of ribavirin (1000–1200 mg, depending on weight <75 or ≥ 75 kg) (some clinicians may wish to adhere to the Food and Drug Administration–approved 800 mg daily dose of ribavirin when used with PEG-IFN alfa-2b, especially in patients who weigh <65 kg), while patients with the more treatment-favorable genotypes 2 and 3 can be treated for only 24 weeks and with only 800 mg of ribavirin daily. Moreover, 12 weeks of

Table 1. Predictors of Response to PEG-IFN Plus Ribavirin Therapy in RCTs Conducted in Previously Untreated, Immunocompetent Patients With Compensated Chronic Hepatitis C

Non-genotype 1
Low HCV RNA levels
Absence of cirrhosis/bridging fibrosis
Duration of therapy (for genotype 1)
Age 40 years or younger
Lighter body weight
Nonblack ethnicity
Adherence
Absence of steatosis on liver biopsy

NOTE. Non-genotype 1 is the most influential predictor of response to standard of care therapy with combination PEG-IFN plus ribavirin. The relative weighting of variables analyzed in RCTs of PEG-IFN/ribavirin combination therapy is presented in the technical review.¹

therapy suffices in patients with genotypes 2 and 3 in whom HCV RNA levels are undetectable at week 4. In the group of patients with genotypes 2 and 3, patients with genotype 2 are more likely than those with genotype 3 to achieve an SVR; for patients with genotype 3 who have high levels of HCV RNA or advanced fibrosis on liver biopsy, many authorities recommend treatment for 48 weeks. Pending additional data, in patients with genotypes 2 and 3, clinicians may wish to consider higher doses of ribavirin or a longer duration of therapy on an individual basis, taking into account considerations such as high viral level, cirrhosis, or delayed response to therapy. For patients with genotype 4, 48 weeks of treatment with PEG-IFN alfa plus full-dose (1000–1200 mg) ribavirin is recommended. The potential added benefit of a broader range (800–1400 mg) of ribavirin weight-based dosing as part of combination therapy with PEG-IFN is currently being studied.

Therapy is indicated for previously untreated patients with chronic hepatitis C, circulating HCV RNA, elevated aminotransferase levels, evidence on liver biopsy of moderate to severe hepatitis grade and stage (METAVIR stage $\geq F2$, Ishak stage ≥ 3 , septal or bridging fibrosis), and compensated liver disease.

Patients with milder histologic changes (METAVIR stage F1, Ishak stage <3) (and normal serum aminotransferase activity; see following text) appear to respond as well as patients with more advanced histologic changes; such patients can be counseled about the reduced risk of disease progression but still can be offered therapy. If a decision is made to defer therapy in patients with mild disease, periodic laboratory and histologic monitoring should be pursued; however, data to support a recommendation on the frequency of histologic monitoring are wanting.

Current contraindications to therapy include decompensated cirrhosis (see following text), pregnancy, uncontrolled depression or severe mental illness, active substance abuse in the absence of concurrent participation in a drug treatment program, advanced cardiac or pulmonary disease, severe cytopenias, poorly controlled diabetes, retinopathy, seizure disorders, immunosuppressive treatment, autoimmune diseases, or other inadequately controlled comorbid conditions.

Monitoring Response to Antiviral Therapy

Baseline and 12-week monitoring of HCV RNA levels should be performed with the same quantitative amplification assay. An early virologic response (EVR), defined as a ≥ 2 -log₁₀ reduction in HCV RNA levels during the first 12 weeks of therapy, is a valuable clinical milestone. In the absence of an EVR, the likelihood of an SVR is 0–3%. If the only goal of therapy is to achieve an SVR, therapy can be discontinued after 12 weeks if an EVR is not achieved. Potentially, histologic benefit can accrue even in the absence of an SVR; therefore, some authorities treat beyond 12 weeks even in patients who have not achieved an EVR. For documentation of a virologic response at the end of therapy (end-of-treatment response) or an SVR ≥ 6 months after completing therapy, a more sensitive quantitative assay with a lower limit of ≤ 50 IU/mL, if available, or a qualitative HCV RNA assay is recommended.

Clinical and virologic monitoring during therapy should be conducted at intervals ranging from once a month to once every 3 months. Frequent hematologic monitoring is necessary to identify marked anemia, neutropenia, and thrombocytopenia; monitoring of thyroid-stimulating hormone level is indicated to identify hypothyroidism or hyperthyroidism.

Management of Side Effects of Antiviral Therapy

Side effects of antiviral therapy are listed in Table 2.

Flu-like side effects of IFN can be managed with acetaminophen or nonsteroidal anti-inflammatory drugs, sleep-promoting agents can be used for insomnia, and antidepressants can be used for depression. For management of neutropenia, dose reduction suffices, and the addition of granulocyte colony-stimulating factor is generally not recommended, although it may be considered in individual cases of severe neutropenia.

Ribavirin is contraindicated in pregnancy, necessitating strict precautions and contraception in women

Table 2. Side Effects of Antiviral Therapy

Related to IFN
Flu-like symptoms
Marrow suppression (especially leukopenia and thrombocytopenia)
Emotional effects (irritability, difficulty concentrating, memory disturbances, depression)
Autoimmune disorders (especially thyroiditis)
Hair loss
Rash
Diarrhea
Sleep disorders
Visual disorders (rarely retinal hemorrhages, especially in diabetic patients and hypertensive patients)
Weight loss
Seizures
Hearing loss
Pancreatitis
Interstitial pneumonitis
Injection site reactions
Related to ribavirin
Hemolytic anemia
Chest congestion, dry cough, and dyspnea
Pruritus
Sinus disorders
Rash
Gout
Nausea
Diarrhea
Teratogenicity

of childbearing age and their sexual partners and in HCV-infected men with female partners of childbearing age. Treatment with ribavirin should be avoided in patients with ischemic cardiovascular and cerebrovascular disease and in patients with renal insufficiency. If anemia occurs, options include ribavirin dose reduction or the addition of erythropoietin.

Approach to Other Patient Populations

Normal aminotransferase activity. Patients with persistently normal ALT levels generally do not progress histologically, while responses to combination antiviral therapy in patients with normal ALT levels are indistinguishable from response rates in patients with elevated ALT activity. Patients with normal ALT activity are candidates for antiviral therapy or for monitoring without intervention, as determined on an individual basis and as influenced by patient factors such as motivation, genotype, histologic activity, and fibrosis.

Cirrhosis. Patients with compensated cirrhosis who can tolerate therapy are candidates for treatment. In patients with decompensated cirrhosis, antiviral therapy is not recommended; instead, referral for liver transplantation is indicated. Although patients with decompensated cirrhosis are not routine candidates for

IFN-based antiviral therapy, attempts to eradicate hepatitis C viremia with progressively escalated, low-dose antiviral therapy before transplantation have met with limited, early success; however, data supporting this approach are insufficient to justify its adoption outside of clinical trials conducted at established centers by experienced investigators.

Previous relapsers and nonresponders. Patients in whom HCV RNA is undetectable during and at the end of therapy but reappears again after completion of therapy (relapsers) are likely to respond and experience a relapse again with a subsequent course of the same therapy. The chance of achieving an SVR in relapsers, however, may be as high as 40%–50% if re-treatment is pursued with more effective therapy. If this group of patients is to be re-treated, ideally, a different, more effective regimen should be used. Therapy with PEG-IFN and ribavirin should be strongly considered for patients who experienced a relapse after a course of standard IFN/ribavirin combination therapy, while a longer duration of therapy in patients who experienced a relapse after 12 months of treatment with PEG-IFN plus ribavirin is of unproven efficacy.

For nonresponders to a previous course of standard IFN monotherapy, re-treatment with PEG-IFN plus ribavirin can increase the frequency of responsiveness to approximately 20%; for nonresponders to a previous course of standard IFN plus ribavirin, re-treatment with PEG-IFN plus ribavirin can increase the frequency of responsiveness to approximately 10%. Expectations for responsiveness to re-treatment are lower in patients with genotype 1, cirrhosis, high baseline HCV RNA levels, and black ethnicity. Such factors, in addition to a patient's tolerance to previous therapy and severity of underlying liver disease, should be taken into consideration when making individualized decisions about the re-treatment of prior nonresponders.

Given the difficulty of clearing hepatitis C viremia, nonresponder patients have been considered as candidates for long-term maintenance therapy. Hypothetically, maintenance IFN α therapy in prior nonresponders might retard the progression of fibrosis and limit the progression of cirrhosis to end-stage liver disease and hepatocellular carcinoma. Therefore, several large, multicenter RCTs of long-term (2–4 years) therapy with low-dose PEG-IFN are in progress to assess the effect of maintenance therapy on histologic and clinical end points in patients with chronic hepatitis C and advanced fibrosis. The results of these trials will be required before recommendations can be made for chronic maintenance therapy in those with

advanced histologic fibrosis who fail to achieve an SVR.

Acute hepatitis C. The risk of HCV infection after an accidental needlestick is sufficiently low to delay antiviral therapy until HCV infection is documented virologically and biochemically. Patients with acute hepatitis C are candidates for antiviral therapy after a period of observation to allow for potential spontaneous clearance. Case series have focused primarily on IFN or PEG-IFN monotherapy administered for 12–24 weeks. Although combination IFN or PEG-IFN/ribavirin has not been shown to be superior to IFN monotherapy, conventional doses of PEG-IFN/ribavirin combination therapy may represent a reasonable approach to treatment of patients with acute hepatitis C. In fact, the optimal regimen, dose, time to initiate therapy, duration of therapy, or benefit of adding ribavirin to IFN therapy has not been established, and the infrequency of acute hepatitis C will likely confound the prospective comparison of different treatment regimens. Based on available data, most authorities would initiate treatment no later than 2–3 months after presentation with acute hepatitis and would extend therapy for at least 24 weeks.

Injection drug or alcohol use. Therapy is recommended for recovered drug users, including those on methadone maintenance, and, based on a case-by-case review, for active drug users, especially when in conjunction with drug treatment programs. Additional randomized trials will be required to evaluate the following: the safest and most effective treatment regimens; the levels of and factors favoring compliance; the risk of recidivism; side effect profiles, including the risk of depression; and the effect of antiviral therapy on methadone requirements.

Abstinence should be recommended before and during antiviral treatment in alcoholic persons, and treatment of alcohol abuse should be linked with efforts to treat hepatitis C in alcoholic patients. A safe level of alcohol consumption in patients with hepatitis C has not been established.

Hematologic disorders. The therapeutic approach in this group of patients may depend on the underlying hematologic disorder. For example, in thalassemic patients, primary therapy should be focused on reducing iron overload. Chronic hepatitis C may be treated with PEG-IFN plus ribavirin, although data supporting the safety and efficacy of ribavirin, at full or reduced doses, in these populations are limited, because registration trials of PEG-IFN plus ribavirin excluded patients with these disorders specifically. In patients with a genetic predisposition

to anemia, ribavirin-associated hemolysis would be predicted to be more severe, transfusion requirements may increase during antiviral therapy, and data providing guidelines for ribavirin dosing are unavailable. Treatment guidelines for hemophiliac patients are the same as those in the nonhemophiliac population. The risk of pretreatment liver biopsy is higher but can be minimized by coordination with hematologic expertise.

Children. For children, the general principles of management are the same as those for adults, except that treatment is not recommended for children younger than 3 years.

End-stage renal disease. Currently, ribavirin is contraindicated in patients with renal failure; however, clinical trials are in progress to assess the safety and efficacy of low-dose ribavirin combined with PEG-IFN. At present, the role of antiviral therapy in patients with end-stage renal disease remains undefined. For individual patients, the potential benefit of therapy should be weighed against the higher risk of toxicity, and treatment should be undertaken in centers with experienced clinicians, ideally in clinical trials. For PEG-IFN alfa-2a, a dose reduction from 180 to 135 μg is recommended by the manufacturer for patients with renal failure; for PEG-IFN alfa-2b, the manufacturer makes no specific recommendation about dose reduction for patients with renal failure, but 50% dose reductions are recommended for other clinical indications (eg, hematologic). Patients with end-stage renal disease and chronic hepatitis C who are candidates for kidney transplantation should be evaluated for advanced hepatic fibrosis, which is associated with reduced graft and patient survival.

Extrahepatic disease. In patients with cutaneous vasculitis and glomerulonephritis resulting from HCV-associated mixed essential cryoglobulinemia, indefinite maintenance therapy may be required. Hepatitis C-associated B-cell lymphoma may respond to antiviral therapy.

Human immunodeficiency virus and HCV coinfection. All patients with human immunodeficiency virus (HIV) infection should be screened for HCV infection; among those with HCV infection, evaluation of candidacy for antiviral therapy should be undertaken (including liver biopsy). Ideally, the HIV infection should be well controlled with antiretroviral therapy before treatment of the HCV infection is initiated. Optimal therapy consists of PEG-IFN alfa at the routine weekly dose plus ribavirin at a daily dose of 600–800 mg (higher if tolerated) for 48 weeks, regardless of genotype. Because of potential drug-drug interactions in patients on HIV

treatment regimens that include didanosine, HIV regimens should be altered in those starting combination therapy for HCV infection. If didanosine is critical to the HIV regimen, ribavirin should be avoided.

Liver transplantation. Results of antiviral therapy for hepatitis C after liver transplantation have been disappointing, and results of clinical trials are mixed at best. Whether begun prophylactically immediately after transplantation to prevent reinfection or initiated to treat established posttransplantation hepatitis C, antiviral therapy, even with combination PEG-IFN alfa and ribavirin, may suppress HCV replication but results in an SVR in <20% of treated patients. Moreover, IFN, PEG-IFN, and ribavirin have not been well tolerated after liver transplantation, necessitating dose reductions for adverse events such as anemia and serious infections. Therefore, after liver transplantation, the risks and benefits of antiviral therapy should be weighed carefully for each patient, and treatment should be initiated with caution by transplantation teams experienced in the treatment of hepatitis C. Because immunosuppression increases HCV replication, which is associated with increased HCV-associated liver injury and may contribute to disease progression, doses of immunosuppressive drugs should be kept to a minimum in patients who undergo liver transplantation for chronic hepatitis C.

Other Therapies

Clinical trials have failed to demonstrate the efficacy of phlebotomy, amantadine, IFN gamma, interleukin-10, or thymosin α -1 in patients with chronic HCV infection, although additional trials for some of these agents are continuing. IFN beta offers no advantage over IFN alfa and is not approved for the treatment of hepatitis C. Currently, none of these can be recommended. Similarly, alternative and complementary therapies have not been proven to be effective in clinical trials and are not recommended.

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References

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The Medical Position Statements (MPS) developed under the aegis of the American Gastroenterological Association (AGA) and its Clinical Practice and Economics Committee (CPEC) were approved by the AGA Governing Board. The data used to formulate these recommendations are derived from the data available at the time of their creation and may be supplemented and updated as new information is assimilated. These recommendations are intended for adult patients, with the intent of suggesting preferred approaches to specific medical issues or problems. They are based upon the interpretation and assimilation of scientifically valid research, derived from a comprehensive review of published literature. Ideally, the intent is to provide evidence based

upon prospective, randomized placebo-controlled trials; however, when this is not possible, the use of experts' consensus may occur. The recommendations are intended to apply to health care providers of all specialties. It is important to stress that these recommendations should not be construed as a standard of care. The AGA stresses that the final decision regarding the care of the patient should be made by the physician with a focus on all aspects of the patient's current medical situation.

This document presents the official recommendations of the American Gastroenterological Association (AGA) on "Management of Hepatitis C." It was approved by the Clinical Practice and Economics Committee on September 17, 2005, and by the AGA Governing Board on November 6, 2005.