Complete Summary

GUIDELINE TITLE

American Gastroenterological Association medical position statement on the management of hepatitis C.

BIBLIOGRAPHIC SOURCE(S)

Dienstag JL, McHutchison JG. American Gastroenterological Association medical position statement on the management of hepatitis C. Gastroenterology 2006 Jan;130(1):225-30. [2 references] PubMed

GUIDELINE STATUS

This is the current release of the guideline.

According to the guideline developer, the Clinical Practice Committee meets three times a year to review all American Gastroenterological Association Institute (AGAI) guidelines. This review includes new literature searches of electronic databases followed by expert committee review of new evidence that has emerged since the original publication date.

**** REGULATORY ALERT ****

FDA WARNING/REGULATORY ALERT

Note from the National Guideline Clearinghouse: This guideline references a drug(s) for which important revised regulatory information has been released.

- July 31, 2008, Erythropoiesis Stimulating Agents (ESAs): Amgen and the U.S. Food and Drug Administration (FDA) informed healthcare professionals of modifications to certain sections of the Boxed Warnings, Indications and Usage, and Dosage and Administration sections of prescribing information for Erythropoiesis Stimulating Agents (ESAs). The changes clarify the FDA-approved conditions for use of ESAs in patients with cancer and revise directions for dosing to state the hemoglobin level at which treatment with an ESA should be initiated.
- November 8, 2007 and January 3, 2008 Update, Erythropoiesis Stimulating Agents (ESAs): The U.S. Food and Drug Administration (FDA) notified healthcare professionals of revised boxed warnings and other safety-related product labeling changes for erythropoiesis-stimulating agents (ESAs) stating serious adverse events, such as tumor growth and shortened survival in patients with advanced cancer and chronic kidney failure.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Hepatitis C

GUIDELINE CATEGORY

Diagnosis
Evaluation
Management
Screening
Treatment

CLINICAL SPECIALTY

Family Practice
Gastroenterology
Infectious Diseases
Internal Medicine

INTENDED USERS

Advanced Practice Nurses
Health Care Providers
Nurses
Physician Assistants
Physicians

GUIDELINE OBJECTIVE(S)

To provide recommendations for preferable approaches to the management of persons with hepatitis C

TARGET POPULATION

Screening

High-risk groups, including:

- Injection drug users
- Persons who received a transfusion before 1992
- Persons with hemophilia who received clotting factors before 1987
- Persons with frequent percutaneous exposures
- Immigrants from countries with a high prevalence of hepatitis C virus (HCV) infection
- Persons with clinical or biochemical evidence for chronic liver disease
- Spouses of persons with chronic hepatitis C infection
- Persons infected with human immunodeficiency virus (HIV)

Management/Treatment

- Hepatitis C virus-infected adults

INTERVENTIONS AND PRACTICES CONSIDERED

Screening

1. Screening of high-risk groups (note: routine screening of all asymptomatic adults is not recommended)

Evaluation/Diagnosis

1. Laboratory testing including
    - Testing for hepatitis C virus (HCV) ribonucleic acid (RNA)
    - HCV genotyping
    - Liver biopsy
    - Liver ultrasonography (considered but not recommended)

Management/Treatment

1. Combination of subcutaneous injection of pegylated interferon (PEG-IFN) alfa and oral ribavirin
2. 48-week treatment for persons with genotype-1 and 4 HCV infection and 24-week treatment for persons with genotype-2 or 3 HCV infection
3. Monitoring HCV RNA levels (response to antiviral therapy)
4. Management of adverse effects of antiviral therapy (acetaminophen, nonsteroidal anti-inflammatory drugs, sleep-promoting agents, antidepressants; in cases of severe neutropenia - granulocyte colony-stimulating factor)

    Note: Routine use of granulocyte colony-stimulating factor is not recommended.

5. Special management considerations for the following patient groups:
    - Patients with normal aminotransferase activity
    - Patients with cirrhosis

- Previous relapsers and nonresponders
- Patients with acute hepatitis C
- Injection drug or alcohol users
- Patients with hematological disorders
- Children with hepatitis C
- Patients with end-stage renal disease
- Patients with extrahepatic disease
- Patients with HIV infection
- Patients who have undergone liver transplantation

Note: The following procedures and medications were considered but not recommended due to the lack of efficacy: phlebotomy, amantadine, IFN gamma, interleukin-10, thymosin alfa-1, interferon beta.

MAJOR OUTCOMES CONSIDERED

- Predictors of treatment response
- Effectiveness of treatment (clinical, histological, and virologic response)
- Side effects of treatment

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

A comprehensive search of electronic databases (including MEDLINE, the Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effectiveness, American College of Physicians Journal Club, *British Medical Journal* Clinical Evidence, EMB Reviews, CINAHL, EMBASE, and HealthSTAR) was performed by a professional evidence-based medicine company to identify relevant articles from 1990 to 2003. The search was restricted to articles involving human studies that were available in English. Additional relevant articles published after the search was completed that were identified by the authors were also included.

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

I Well-designed randomized controlled trials (RCTs)

II-1a Well-designed controlled trials with pseudorandomization

II-1b Well-designed controlled trials with no randomization

II-2a Well-designed cohort (prospective) study with concurrent controls

II-2b Well-designed cohort (prospective) study with historical controls

II-2c Well-designed cohort (retrospective) study with concurrent controls

II-3 Well-designed case-control (retrospective) study

III Large differences from comparisons between times and/or places with and without intervention (in some circumstances these may be equivalent to level II or I)

IV Opinions of respected authorities based on clinical experience; descriptive studies; reports of expert committees

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

The data used to formulate these recommendations are derived from the data available at the time of their creation. 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.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

The document was approved by the Clinical Practice and Economics Committee on September 17, 2005, and by the American Gastroenterological Association (AGA) Governing Board on November 6, 2005.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Screening

Routine screening of all asymptomatic adults, who have a low prior probability of hepatitis C virus (HCV) infection, is not recommended. Among high-risk groups (e.g., 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 ribonucleic acid (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 $\geq$3, METAVIR stage $\geq$F2; please see "American Gastroenterological Association (AGA) Technical Review on the Management of Hepatitis C" 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-microgram/kg dose, and (2) PEG IFN alfa-2a, administered at a fixed, 180-microgram 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 the Table below.

Table. 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.

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 $\geq$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 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 $\geq$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) 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, 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 $\geq$2-$\log_{10}$ 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 $\geq$6 months after completing therapy, a more sensitive quantitative assay with a lower limit of $\leq$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

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 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. Refer to "Potential Harms" field for more information regarding side effects of IFN and ribavirin.

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% to 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 alfa 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 to 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 to 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 to 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 micrograms 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 (e.g., 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 alpha-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.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The strength of the evidence upon which the statements are based is noted in the technical review paper accompanying the original guideline document, with prospective, randomized, controlled trials being the strongest. When adequate data are absent, expert consensus is used and is identified as such.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Improved diagnosis and treatment of hepatitis C virus (HCV) infection

POTENTIAL HARMS

Side Effects of Antiviral Therapy

Interferon

- 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

Ribavirin

- Hemolytic anemia
- Chest congestion, dry cough, and dyspnea
- Pruritus
- Sinus disorders
- Rash
- Gout
- Nausea
- Diarrhea
- Teratogenicity

CONTRAINDICATIONS

CONTRAINDICATIONS

- Current contraindications to *antiviral therapy* include decompensated cirrhosis, 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.
- *Ribavirin* is contraindicated in pregnancy, necessitating strict precautions and contraception in women of childbearing age and their sexual partners and in hepatitis C virus (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.
- *Ribavirin* is currently contraindicated in patients with renal failure.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

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 healthcare 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.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Dienstag JL, McHutchison JG. American Gastroenterological Association medical position statement on the management of hepatitis C. Gastroenterology 2006 Jan;130(1):225-30. [2 references] PubMed

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2006 Jan

GUIDELINE DEVELOPER(S)

American Gastroenterological Association Institute - Medical Specialty Society

SOURCE(S) OF FUNDING

American Gastroenterological Association Institute

GUIDELINE COMMITTEE

American Gastroenterological Association Clinical Practice Committee

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Authors: Jules L. Dienstag; J.G. McHutchison

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Dr. Dienstag serves currently on scientific advisory boards and/or data monitoring committees for Achillion Pharmaceuticals, Bristol-Myers Squibb, Genzyme, Gilead Sciences, Idenix Pharmaceuticals, Metabasis Therapeutics, Nucleonics, Oxxon Therapeutics, SciClone, and Vertex.

Dr. McHutchison has served on scientific advisory boards, speakers bureaus, or as a consultant for Amgen, Anadys Pharmaceuticals, Centocor, GlaxoSmithKline, Idenix, InterMune Pharmaceuticals, Isis Pharmaceuticals, National Genetics Institute, Novartis Pharmaceuticals, Pfizer Pharmaceuticals, Prometheus Laboratories, Ribozyme Pharmaceuticals, Schering-Plough Corporation, Vertex Pharmaceuticals, and XTL; he has received research support from Akros Pharma, Amgen, Bayer Pharmaceuticals, Bio-Medicines, Bristol-Myers Squibb, Coley Pharmaceuticals, Fujisawa, Gilead Sciences, Human Genome Sciences, IDUN, Isis Pharmaceuticals, Ortho Diagnostic Systems, Prometheus Laboratories, Ribozyme Pharmaceuticals, Roche Pharmaceuticals, Schering-Plough Corporation, SciClone, Triangle Pharmaceuticals, and Vertex Pharmaceuticals.

GUIDELINE STATUS

This is the current release of the guideline.

According to the guideline developer, the Clinical Practice Committee meets three times a year to review all American Gastroenterological Association Institute (AGAI) guidelines. This review includes new literature searches of electronic databases followed by expert committee review of new evidence that has emerged since the original publication date.

GUIDELINE AVAILABILITY

Electronic copies: Available from the American Gastroenterological Association Institute (AGAI) *Gastroenterology* journal Web site.

Print copies: Available from the American Gastroenterological Association Institute, 4930 Del Ray Avenue, Bethesda, MD 20814.

AVAILABILITY OF COMPANION DOCUMENTS

The following is available:

- American Gastroenterological Association technical review on the management of hepatitis C. Gastroenterology 2006 Jan;130(1);231-264.

Electronic copies: Available from the American Gastroenterological Association Institute (AGAI) *Gastroenterology* journal Web site.

Print copies: Available from American Gastroenterological Association Institute, 4930 Del Ray Avenue, Bethesda, MD 20814.

PATIENT RESOURCES

None available

NGC STATUS

This summary was completed by ECRI on February 22, 2006. The information was verified by the guideline developer on February 28, 2006. This summary was updated by ECRI on January 29, 2007, following the U.S. Food and Drug Administration advisory on erythropoiesis stimulating agents. This summary was updated by ECRI Institute on July 9, 2007, following the FDA advisory on erythropoiesis stimulating agents. This summary was updated by ECRI Institute on November 9, 2007, following the U.S. Food and Drug Administration advisory on Antidepressant drugs. This summary was updated by ECRI Institute on March 21, 2008 following the FDA advisory on Erythropoiesis Stimulating Agents. This summary was updated by ECRI Institute on August 15, 2008 following the U.S. Food and Drug Administration advisory on Erythropoiesis Stimulating Agents (ESAs).

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Date Modified: 11/3/2008