

Errata

In the practice guideline “Diagnosis, Management, and Treatment of Hepatitis C: An Update ” (HEPATOLOGY 2009;49 (4): 1335-1374; DOI: 10.1002/hep.22759), two errors have been corrected in the online version.

1. The Treatment Objectives and Outcomes section contained an error which has been corrected to read: “Short-term outcomes can be measured biochemically (normalization of serum ALT levels), virologically (absence of HCV RNA from serum by a sensitive PCR based assay), and histologically (>2 point improvement in necroinflammatory score with no worsening in fibrosis score).^{71,72}”
2. In Table 11, the following sentence has been deleted from the second bullet: “Candidates should be abstinent for a minimum period of 6 months.”

Diagnosis, Management, and Treatment of Hepatitis C: An Update

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This document has been approved by the AASLD, the Infectious Diseases Society of America, and the American College of Gastroenterology.

Preamble

These recommendations provide a data-supported approach to establishing guidelines. They are based on the following: (1) a formal review and analysis of the recently published world literature on the topic (Medline search up to September 2008); (2) the American College of Physicians' *Manual for Assessing Health Practices and Designing Practice Guidelines*;¹ (3) guideline policies, including the American Association for the Study of Liver Diseases' (AASLD) Policy on the Development and Use of Practice Guidelines and the American Gastroenterological Association's Policy Statement on the Use of Medical Practice Guidelines;² and (4) the experience of the authors in regard to hepatitis C.

Abbreviations: AASLD, American Association for the Study of Liver Diseases; ALT, alanine aminotransferase; ANC, absolute neutrophil count; anti-HCV, antibody to HCV; AST, aspartate aminotransferase; CKD, chronic kidney disease; CTP, Child-Turcotte-Pugh; ELA, enzyme immunoassay; ETR, end-of-treatment response; EVR, early virological response; FDA, U.S. Food and Drug Administration; HCV, hepatitis C virus; HIV, human immunodeficiency virus; PCR, polymerase chain reaction; PEG, polyethylene glycol; RVR, rapid virological response; SVR, sustained virological response; ULN, upper limit of normal.

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Received November 21, 2008; accepted November 23, 2008.

Disclaimer Statement: The views expressed in these guidelines do not necessarily represent the views of the Department of Health and Human Services, the National Institutes of Health, the National Institute of Diabetes and Digestive and Kidney Diseases, or the United States Government.

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Published online in Wiley InterScience (www.interscience.wiley.com).

DOI 10.1002/hep.22759

Potential conflict of interest: Drs. Marc Ghany, Leonard Seeff, and Doris Strader have no financial relationships to declare. Dr. David Thomas was on the Advisory Board of Merck, Sharpe and Dohme at the time of writing but has since resigned from this position.

All American Association for the Study Liver Diseases (AASLD) Practice Guidelines are updated annually. If you are viewing a Practice Guideline that is more than 12 months old, please visit www.aasld.org for an update in the material.

Intended for use by physicians, these recommendations suggest preferred approaches to the diagnostic, therapeutic and preventive aspects of care. They are intended to be flexible, in contrast to standards of care, which are inflexible policies to be followed in every case. Specific recommendations are based on relevant published information. To more fully characterize the quality of evidence supporting recommendations, the Practice Guidelines Committee of the AASLD requires a Class (reflecting benefit versus risk) and Level (assessing strength or certainty) of Evidence to be assigned and reported with each recommendation (Table 1, adapted from the American College of Cardiology and the American Heart association Practice Guidelines).^{3,4}

Background

The hepatitis C virus (HCV) is a major public health problem and a leading cause of chronic liver disease.⁵ An estimated 180 million people are infected worldwide.⁶ In the United States (U.S.), the prevalence of HCV infection between the years 1999 and 2002 was 1.6%, equating to about 4.1 million persons positive for antibody to hepatitis C (anti-HCV), 80% of whom are estimated to be viremic.⁷ Hepatitis C is the principal cause of death from liver disease and the leading indication for liver transplantation in the U.S.⁸ Some calculations suggest that mortality related to HCV infection (death from liver failure or hepatocellular carcinoma) will continue to increase over the next two decades.⁹ The purpose of this document is to provide clinicians with evidence-based approaches to the prevention, diagnosis, and management of HCV infection.

Testing and Counseling

Testing. The optimal approach to detecting HCV infection is to screen persons for a history of risk of exposure to the virus, and to test selected individuals who have an identifiable risk factor.¹⁰ Currently, injection drug use is the primary mode of HCV transmission in the U.S.; thus, all persons who use or have used illicit injection drugs in the present or past, even if only once, as well as intranasal drug users who share paraphernalia, should be tested for HCV infection.^{7,11,12} Individuals who have received a blood or blood component transfusion or an

Table 1. Grading System for Recommendations

Classification	Description
Class I	Conditions for which there is evidence and/or general agreement that a given diagnostic evaluation procedure or treatment is beneficial, useful, and effective.
Class II	Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a diagnostic evaluation, procedure or treatment.
Class IIa	Weight of evidence/opinion is in favor of usefulness/efficacy.
Class IIb	Usefulness/efficacy is less well established by evidence/opinion.
Class III	Conditions for which there is evidence and/or general agreement that a diagnostic evaluation, procedure/treatment is not useful/effective and in some cases may be harmful.

Level of Evidence	Description
Level A	Data derived from multiple randomized clinical trials or meta-analyses.
Level B	Data derived from a single randomized trial, or nonrandomized studies.
Level C	Only consensus opinion of experts, case studies, or standard-of-care.

organ transplant before 1992 should also be tested. With the introduction of sensitive tests to screen blood donors for HCV antibodies in 1992, transfusion-transmission of HCV has become rare.^{12,13} Persons with hemophilia should be tested for HCV infection if blood products were received before 1987, after which time, viral inactivation procedures were implemented.¹⁴ Similarly, individuals with unexplained elevations of the aminotransferase levels (alanine and/or aspartate aminotransferase; ALT/AST), those ever on hemodialysis, children born to HCV-infected mothers, or those with human immunodeficiency virus (HIV) infection should be tested for the presence of HCV infection.¹⁵⁻¹⁷

Other potential sources of HCV transmission include exposure to an infected sexual partner or multiple sexual partners, exposure among health care workers to HCV-contaminated blood and blood products, and tattooing.^{12,15,18-23} The prevalence of HCV infection is consistently higher among persons with multiple sexual partners, whereas sexual transmission of HCV between monogamous partners is uncommon.^{11,18} Thus, although it is prudent to counsel HCV-infected persons to notify their current partners of their HCV status, they should be informed that the risk of sexual transmission is sufficiently low¹⁹ that many authorities do not advise the use of barrier protection among monogamous couples.¹⁸ Nevertheless, between 1% and 5% of monogamous sexual partners of index HCV cases test positive for anti-HCV. There is no need for HCV-infected persons to limit ordinary household activities except for those that might result in blood exposure, such as sharing a razor or toothbrush.

The hepatitis C virus is not transmitted by hugging, kissing, sharing of eating utensils or breastfeeding.

Folk medicine practices, including acupuncture and ritual scarification, as well as body piercing, tattooing and commercial barbering are potential modes for transmission of HCV infection when performed without appropriate infection control measures.²⁴⁻²⁸ Transmission of HCV infection by body piercing is, however, rare and many HCV infected persons who have undergone body piercing acquired their infection by other means.^{23,29-33} Therefore, there is no need to routinely test persons who have received tattoos or undergone piercings in the absence of other risk factors, particularly if these procedures have taken place in licensed establishments. Because symptoms are generally absent in individuals with chronic HCV infection, recognition of infection requires risk factor screening, which should be done whenever it is possible to link with appropriate HCV testing and counseling.¹⁰

Table 2 outlines the list of persons who should be routinely screened for HCV infection.¹⁵ For some groups, such as those with a history of injection drug use or persons with hemophilia, the prevalence of HCV is high ($\approx 90\%$). For other groups (recipients of blood transfusions prior to 1992), the prevalence is moderate ($\approx 10\%$). For still others, (persons with needle stick exposure, sexual partners of HCV-infected persons), the prevalence is low (1% to 5%).

Table 2. Persons for Whom HCV Screening is Recommended

- | |
|---|
| <ul style="list-style-type: none"> ● 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: <ul style="list-style-type: none"> ○ Persons with HIV infection ○ Persons with hemophilia who received clotting factor concentrates prior to 1987 ○ Persons who have ever been on hemodialysis ○ Persons with unexplained abnormal aminotransferase levels ● Prior recipients of transfusions or organ transplants prior to July 1992 including: <ul style="list-style-type: none"> ○ 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 ○ Persons who received an organ transplant ● 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* |
|---|

Table adapted from "Recommendations for prevention and control of hepatitis C virus (HCV) infection and HCV-related chronic disease." Centers for Disease Control and Prevention. MMWR Recomm Rep 1998;47(RR-19):1-39.

*Although the prevalence of infection is low, a negative test in the partner provides reassurance, making testing of sexual partners of benefit in clinical practice.

Table 3. Measures to Avoid Transmission of HCV

- HCV-infected persons should be counseled to avoid sharing toothbrushes and dental or shaving equipment, and be cautioned to cover any bleeding wound in order to prevent contact of their blood with others
- Persons should be counseled to stop using illicit drugs. Those who continue to inject drugs should be counseled to avoid reusing or sharing syringes, needles, water, cotton or other paraphernalia; to clean the injection site with a new alcohol swab; and to dispose of syringes and needles after one use in a safe, puncture-proof container
- HCV-infected persons should be advised to not donate blood, body organs, other tissue or semen
- HCV-infected persons should be counseled that the risk of sexual transmission is low, and that the infection itself is not a reason to change sexual practices (i.e., those in long-term relationships need not start using barrier precautions and others should always practice "safer" sex)

Table adapted from "Recommendations for prevention and control of hepatitis C virus (HCV) infection and HCV-related chronic disease." Centers for Disease Control and Prevention. MMWR Recomm Rep 1998;47(RR-19):1-39.

Recommendation

1. As part of a comprehensive health evaluation, all persons should be screened for behaviors that place them at high risk for HCV infection. (Class I, level B).

2. Persons who are at risk should be tested for the presence of HCV infection (Table 2) (Class I, level B).

Counseling. Good clinical practice dictates that persons found to be HCV-infected are counseled regarding prevention of spread of the virus to others. Because exposure to infected blood is the primary mode of transmission, it is essential to inform HCV-infected individuals that precautions should be taken to avoid the possibility of exposing others to contact with their blood. This is particularly important for injection drug users who are the leading source of HCV infection, because their transmission route is primarily via sharing of needles and other infected implements. Table 3 outlines the measures to avoid HCV transmission.

Recommendation

3. Persons infected with HCV should be counseled on how to avoid HCV transmission to others, as indicated in Table 3 (Class I, level C)

Laboratory Testing

Two classes of assays are used in the diagnosis and management of HCV infection: serologic assays that detect specific antibody to hepatitis C virus (anti-HCV) and molecular assays that detect viral nucleic acid. These assays have no role in the assessment of disease severity or prognosis.

Serologic Assays. Tests that detect anti-HCV are used both to screen for and to diagnose HCV infection. Anti-HCV can be detected in the serum or plasma using a number of immunoassays. Two enzyme immunoassays (EIAs) are approved by the U.S. Food and Drug Administration (FDA) for clinical use, Abbott HCV EIA 2.0 (Abbott Laboratories, Abbott Park, IL) and ORTHO® HCV Version 3.0 ELISA (Ortho-Clinical Diagnostics, Raritan, NJ), as well as one enhanced chemiluminescence immunoassay (CIA) VITROS® Anti-HCV assay, (Ortho-Clinical Diagnostics, Raritan, NJ). The specificity of current EIAs for anti-HCV is greater than 99%.³⁴ False positive results are more likely to occur when testing is performed among populations where the prevalence of hepatitis C is low. False negative results may occur in the setting of severe immunosuppression such as infection with HIV, solid organ transplant recipients, hypo- or agammaglobulinemia or in patients on hemodialysis.³⁵⁻³⁷ The recombinant immunoblot assay, Chiron RIBA HCV 3.0 SIA (Chiron Corporation, Emeryville, CA) is also FDA approved. This assay was originally developed as a more specific, supplemental assay to confirm the results of EIA testing.^{38,39} However, specificity is extremely high for third generation EIA results that exceed particular signal/cutoff ratios (e.g., >3.8 for the above mentioned Ortho and Abbott EIA tests). Given the widespread availability of nucleic acid testing, the role for RIBA testing in HCV diagnosis and management has all but disappeared.^{40,41}

Molecular Assays. The list of commercial assays available for the detection (qualitative assays) or quantification (quantitative assays) of HCV RNA is shown in Tables 4 and 5. Historically, qualitative assays have been

Table 4. FDA Approved Qualitative Assays for Detection of HCV RNA

Assay and Manufacturer	Method	Lower Limit of Detection IU/mL	Setting
Amplicor HCV v2.0 (Roche Molecular Systems)	Manual RT-PCR	50	Diagnosis and monitoring
Cobas Amplicor HCV v2.0 (Roche Molecular Systems)	Semi-automated RT-PCR	50	Diagnosis and monitoring
Ampliscreen (Roche Molecular Systems)	Semi-automated RT-PCR	<50	Blood screening
Versant HCV RNA Qualitative Assay, (Siemens Healthcare Diagnostics)	Semi-automated TMA	10	Diagnosis and monitoring
Procleix HIV-1/HCV Assay (Chiron Corporation)	Manual TMA	<50	Blood screening

Abbreviations: RT-PCR, reverse transcription polymerase chain reaction; TMA, transcription-mediated amplification

Table 5. Available Assays for Quantification of HCV in Serum/Plasma

Assay (Manufacturer)	Method	IU/mL Conversion Factor	Dynamic Range (IU/mL)	FDA Approved
Amplicor HCV Monitor (Roche Molecular Systems)	Manual RT-PCR	0.9 copies/mL	600-500,000	Yes
Cobas Amplicor HCV Monitor V2.0 (Roche Molecular Systems)	Semi-automated RT-PCR	2.7 copies/mL	600-500,000	Yes
Versant HCV RNA 3.0 Assay (bDNA) (Siemens Health Care Diagnostics)	Semi-automated bDNA signal amplification	5.2 copies/mL	615-7,700,000	Yes
LCx HCV RNA-Quantitative Assay (Abbott Diagnostics)	Semi-automated RT-PCR	3.8 copies/mL	25-2,630,000	No
SuperQuant (National Genetics Institute)	Semi-automated RT-PCR	3.4 copies/mL	30-1,470,000	No
Cobas Taqman HCV Test (Roche Molecular Systems)	Semi-automated real-time PCR		43-69,000,000	Yes
Abbott RealTime (Abbott Diagnostics)	Semi-automated RT-PCR		12-100,000,000	No

more sensitive than quantitative assays. With the recent availability of real time polymerase chain reaction (PCR)-based assays and transcription-mediated amplification (TMA) assays, with sensitivities of 10-50 IU/mL, there is no longer need for qualitative assays.^{42,43} A highly sensitive assay with this lower limit of detection is considered appropriate for monitoring during therapy. All currently available assays have excellent specificity, in the range of 98% to 99%. In 1997, the World Health Organization established the first International standard for HCV RNA nucleic acid technology,⁴⁴ and the IU rather than viral copies is now the preferred unit to report test results.^{44,45} For monitoring purposes, it is important to use the same laboratory test before and during therapy.

Genotyping Assays. Genotyping is useful in epidemiological studies and in clinical management for predicting the likelihood of response and determining the optimal duration of therapy. The hepatitis C virus can be classified into at least 6 major genotypes (genotypes 1 to 6) based on a sequence divergence of 30% among isolates.⁴⁶ Genotype 1 (subtypes 1a and 1b) is the most common in the U.S., followed by genotypes 2 and 3. Less common genotypes (genotypes 4-6) are beginning to be observed more frequently because of the growing cultural diversity within the United States.⁴⁷ Several commercial assays are available to determine HCV genotypes using direct sequence analysis of the 5' non-coding region, that include Trugene 5'NC HCV Genotyping kit (Siemens Healthcare Diagnostics Division, Tarrytown, NY), reverse hybridization analysis using genotype specific oligonucleotide probes located in the 5' non-coding region, INNO-LiPa HCV II, (Innogenetics, Ghent, Belgium), and Versant HCV Genotyping Assay 2.0 (Siemens Healthcare Diagnostics Division, Tarrytown, NY). Incorrect typing among the major genotypes is rare (<3%) and mixed genotypes occur but are uncommon. Occa-

sionally (<5%), tested samples cannot be genotyped. This usually results from low viral levels, issues with the PCR amplification step of the assay, or extreme nucleotide variability within the HCV genome.⁴⁸

Diagnosis of Acute and Chronic HCV Infection and Interpretation of Assays

The diagnosis of acute or chronic HCV infection generally requires testing of serum for both antibody to HCV (anti-HCV) and for HCV RNA. A sensitive quantitative HCV RNA assay is recommended for diagnosis because it also provides information on the level of virus which is helpful in management.

The differentiation of acute from chronic HCV infection depends on the clinical presentation: namely the presence of symptoms or jaundice, and whether or not there was a prior history of ALT elevation and its duration. After acute exposure, HCV RNA is usually detected in serum before antibody; HCV RNA can be identified as early as 2 weeks following exposure whereas anti-HCV is generally not detectable before 8-12 weeks. These two markers of HCV infection may be present in varying permutations, requiring careful analysis for interpretation (Table 6).

Table 6. Interpretation of HCV Assays

Anti-HCV	HCV RNA	Interpretation
Positive	Positive	Acute or chronic HCV depending on the clinical context
Positive	Negative	Resolution of HCV; Acute HCV during period of low-level viremia.
Negative	Positive	Early acute HCV infection; chronic HCV in setting of immunosuppressed state; false positive HCV RNA test
Negative	Negative	Absence of HCV infection

Table 7. Comparison of Scoring Systems for Histological Stage

Stage	IASL ⁵¹	Batts-Ludwig ⁵²	Metavir ⁵³	Ishak ⁵⁴
0	No fibrosis	No Fibrosis	No fibrosis	No fibrosis
1	Mild fibrosis	Fibrous portal expansion	Periportal fibrotic expansion	Fibrous expansion of some portal areas with or without short fibrous septa
2	Moderate fibrosis	Rare bridges or septae	Periportal septae 1 (septum)	Fibrous expansion of most portal areas with or without short fibrous septa
3	Severe fibrosis	Numerous bridges or septae	Porto-central septae	Fibrous expansion of most portal areas with occasional portal to portal bridging
4	Cirrhosis	Cirrhosis	Cirrhosis	Fibrous expansion of most portal areas with marked bridging (portal to portal and portal to central)
5				Marked bridging (portal to portal and portal to central) with occasional nodules (incomplete cirrhosis)
6				Cirrhosis

One pattern is the identification of both anti-HCV and HCV RNA in a person with recent elevation of the ALT value. This scenario is consistent with either acute HCV infection when there is a recent known risk exposure, with exacerbation of chronic HCV infection, or with an acute hepatitis of another etiology in a patient with chronic HCV infection. Another pattern is the detection of anti-HCV but with a negative test for HCV RNA. This may represent acute HCV infection during a period of transient clearance of HCV RNA, a false positive or negative result or, more commonly, recovery from HCV infection. Re-testing for HCV RNA 4-6 months later is recommended to confirm the resolution of HCV infection. The reverse scenario — a negative anti-HCV test but a positive result for HCV RNA — is compatible with the early stage of acute infection prior to the development of antibody or may represent chronic infection in an immunosuppressed individual. Alternatively, it may represent a false positive HCV RNA result. In all circumstances, re-testing for anti-HCV and HCV RNA in 4-6 months should resolve the issue. Finally, if the patient has raised ALT values but the tests for anti-HCV and HCV RNA are negative, both acute and chronic hepatitis C may be excluded and another diagnosis should be considered. Antibody testing should be repeated in 4-6 months for confirmation purposes.

Recommendation

4. Patients suspected of having acute or chronic HCV infection should first be tested for anti-HCV (Class I, Level B).

5. HCV RNA testing should be performed in:

a) Patients with a positive anti-HCV test (Class I, Level B)

b) Patients for whom antiviral treatment is being considered, using a sensitive quantitative assay (Class I, Level A)

c) Patients with unexplained liver disease whose anti-HCV test is negative and who are immunocom-

promised or suspected of having acute HCV infection (Class I, Level B).

6. HCV genotyping should be performed in all HCV-infected persons prior to interferon-based treatment in order to plan for the dose and duration of therapy and to estimate the likelihood of response (Class I, Level A)

Utility of the Liver Biopsy and Noninvasive Tests of Fibrosis

There are three primary reasons for performing a liver biopsy: it provides helpful information on the current status of the liver injury, it identifies features useful in the decision to embark on therapy, and it may reveal advanced fibrosis or cirrhosis that necessitates surveillance for hepatocellular carcinoma (HCC) and/or screening for varices. The biopsy is assessed for grade and stage of the liver injury, but also provides information on other histological features that might have a bearing on liver disease progression.⁴⁹ The grade defines the extent of necroinflammatory activity, while the stage establishes the extent of fibrosis or the presence of cirrhosis. Several scoring systems have been conceived, the most common being the French METAVIR, the Batts-Ludwig, the International Association for the Study of the Liver (IASL) and the Ishak Scoring systems.⁵⁰⁻⁵⁴ (Table 7). The two more common non-HCV conditions that might affect disease progression and possibly impede treatment response are steatosis^{49,55,56} and excess hepatocellular iron.⁵⁷ Identifying either of these two features does not preclude initiating treatment, but their presence provides additional information regarding the likelihood of response to treatment.⁵⁸⁻⁶⁰

The liver biopsy has been widely regarded as the “gold standard” for defining the liver disease status, but it has drawbacks that have prompted questions about its value.^{61,62} The procedure is not without risks (including pain, bleeding and perforation of other organs),^{63,64} it is

subject to sampling error,⁶⁵ it requires special expertise for interpreting the histopathology, it adds cost to medical care, and it is anxiety-provoking for the implicated person. Thus, efforts are underway to seek alternative means of establishing information on the extent of fibrosis by focusing on noninvasive blood marker panels.⁶⁶ These markers are useful for establishing the two ends of the fibrosis spectrum (minimal fibrosis and cirrhosis) but are less helpful in assessing the mid-ranges of fibrosis or for tracking fibrosis progression.⁶⁶ The recently developed transient elastography that uses ultrasound and low frequency elastic waves to measure liver elasticity⁶⁷ has improved the ability to define the extent of fibrosis without a liver biopsy, particularly when combined with other noninvasive markers.⁶⁸ However, it is not yet ready to replace the liver biopsy since it is not FDA approved, the failure rate is higher in obese patients, and there is now evidence that the transient elastography score can be unexpectedly increased in persons with acute hepatitis who have high necroinflammatory activity but no or minimal fibrosis.^{69,70}

A liver biopsy may be unnecessary in persons with genotypes 2 and 3 HCV infection, since more than 80% of them achieve a sustained virological response (SVR) to standard-of-care treatment. There is, however, an ongoing debate about whether a biopsy is warranted for persons infected with HCV, genotype 1, whose response to such treatment approximates 50% among Caucasians and 30% among African Americans.⁷¹⁻⁷³ Even more uncertain is whether there is need for a liver biopsy in persons infected with the other less common genotypes (4 through 6).

Thus, although the liver biopsy was previously regarded as routine for defining the fibrosis stage in persons with genotype 1 infection,⁶² the issue is now in a state of flux and possible transition. Supporters of a biopsy cite the difficult nature and high cost of current antiviral therapy and are therefore willing to withhold or delay treatment if liver histology displays minimal to moderate fibrosis stage ≤ 2 (Table 7), especially if the infection is known to have been long-standing. These individuals are regarded as having slowly progressive liver disease that may not be responsible for their ultimate demise⁷⁴⁻⁷⁶ However, treatment is advised for those with more advanced fibrosis stage ≥ 3 (Table 7) It must be noted, however, that while information obtained from a biopsy is useful, the procedure is not mandatory for deciding on treatment. If performed and treatment is withheld, a common strategy is to repeat the liver biopsy 4 to 5 years later and to reconsider treatment should there be evidence of disease progression.⁷⁷

The earlier views that persons with genotype 1 infection and persistently *normal* aminotransferase values did not require a liver biopsy because they were believed to have minimal liver disease, and that treatment may actually be harmful, are no longer valid.⁷⁸ It is now apparent that as many as a quarter of such individuals have significant fibrosis,⁷⁸⁻⁸¹ and that treatment response is similar to that of individuals with abnormal serum aminotransferase levels.⁸²⁻⁸⁴ Therefore, the decision to perform a liver biopsy should be based on whether treatment is being considered, taking into account the estimated duration of infection and other indices of advancing liver disease (e.g., the platelet count), the viral genotype, and the patient's willingness to undergo a liver biopsy and motivation to be treated. If the biopsy is not performed and treatment not undertaken, the patient should continue to be monitored at least annually and a biopsy performed if the aminotransferase values become abnormal and other indicators of progressing liver disease become apparent.

Recommendations

7. A liver biopsy should be considered in patients with chronic hepatitis C infection if the patient and health care provider wish information regarding fibrosis stage for prognostic purposes or to make a decision regarding treatment (Class IIa, Level B)

8. Currently available noninvasive tests may be useful in defining the presence or absence of advanced fibrosis in persons with chronic hepatitis C infection, but should not replace the liver biopsy in routine clinical practice (Class IIb, Level C).

Initial Treatment of HCV Infection

Justification for Treatment. Natural history studies indicate that 55% to 85% of individuals who develop acute hepatitis C will remain HCV-infected.^{76,85,86} Spontaneous resolution is more common among infected infants and young women than among persons who are older when they develop acute hepatitis.⁸⁶ Chronic HCV infection has relevance for the infected persons as well as for their contacts: the former are at risk for progression to cirrhosis and/or HCC, the latter are at risk of acquiring the infection through exposure to the virus. The risk of developing cirrhosis ranges from 5% to 25% over periods of 25 to 30 years.^{87,88} Prospective studies of women and children infected at a young age and followed for 20 to 30 years report low rates of cirrhosis, 1% to 3%.^{75,89-92} Retrospective studies of patients referred to tertiary care facilities document higher rates of cirrhosis, 20% to 25%, but this figure may be inflated by referral bias.^{93,94} Progression to cirrhosis may be accelerated in persons who are of older

Table 8. Virological Responses During Therapy and Definitions

Virological Response	Definition	Clinical Utility
Rapid virological response (RVR)	HCV RNA negative at treatment week 4 by a sensitive PCR-based quantitative assay	May allow shortening of course for genotypes 2&3 and possibly genotype 1 with low viral load
Early virological response (EVR)	≥ 2 log reduction in HCV RNA level compared to baseline HCV RNA level (partial EVR) or HCV RNA negative at treatment week 12 (complete EVR)	Predicts lack of SVR
End-of-treatment response (ETR)	HCV RNA negative by a sensitive test at the end of 24 or 48 weeks of treatment	
Sustained virological response (SVR)	HCV RNA negative 24 weeks after cessation of treatment	Best predictor of a long-term response to treatment
Breakthrough	Reappearance of HCV RNA in serum while still on therapy	
Relapse	Reappearance of HCV RNA in serum after therapy is discontinued	
Nonresponder	Failure to clear HCV RNA from serum after 24 weeks of therapy	
Null responder	Failure to decrease HCV RNA by < 2 logs after 24 week of therapy	
Partial responder	Two log decrease in HCV RNA but still HCV RNA positive at week 24	

age, who are obese, who are immunosuppressed (e.g., HIV co-infected), and who consume more than 50g of alcohol per day, although the precise quantity of alcohol associated with fibrosis progression is unknown.⁹⁵⁻⁹⁸ Persons with HCV-related cirrhosis are at risk for the development of hepatic decompensation (30% over 10 years) as well as hepatocellular carcinoma (1% to 3% per year).⁹⁹

Identifying individuals at risk for developing progressive disease is difficult. Presently, the preferred approach is to assess the degree of fibrosis on liver biopsy, using a validated staging system such as the Ishak, IASL, Metavir or Batts-Ludwig staging systems.^{94,96,100} Persons with no or minimal fibrosis (Ishak stage 0-2; Metavir, IASL and Batts-Ludwig stage 0-1) have a low risk for liver-related complications and liver-related death (over the next 10 to 20 years). However, the presence of bridging fibrosis (for example Metavir stage 3, Table 7) is an important predictor of future progression to cirrhosis and therefore an indication for treatment.¹⁰¹

Infection with HCV can also cause extrahepatic diseases including mixed cryoglobulinemia, types II and III. Indeed, symptomatic cryoglobulinemia is an indication for HCV antiviral therapy regardless of the stage of liver disease. (See section on Treatment of Patients with Kidney Disease).

Treatment Objectives and Outcomes. The goal of therapy is to prevent complications and death from HCV infection. Because of the slow evolution of chronic HCV infection over several decades, it has been difficult to demonstrate that therapy prevents complications of liver disease. Accordingly, treatment responses are defined by a surrogate virological parameter rather than a clinical endpoint. Short-term outcomes can be measured biochemically (normalization of serum ALT levels), virologically

(absence of HCV RNA from serum by a sensitive PCR-based assay), and histologically (>2 point improvement in necroinflammatory score with no worsening in fibrosis score).^{71,72} Several types of virological responses may occur, labeled according to their timing relative to treatment. The most important is the sustained virological response (SVR), defined as the absence of HCV RNA from serum by a sensitive PCR assay 24 weeks following discontinuation of therapy (Table 8, Fig. 1). This is generally regarded as a "virological cure," although liver cancer has been identified years later, especially if cirrhosis existed at the time of achieving an SVR.¹⁰²

Undetectable virus at the end of either a 24-week or 48-week course of therapy is referred to as an end-of-treatment response (ETR). An ETR does not accurately predict that an SVR will be achieved but is necessary for it to occur.

A rapid virological response (RVR), defined as undetectable HCV RNA at week 4 of treatment, using a sensitive test with a lower limit of detection of 50 IU/mL, predicts a high likelihood of achieving an SVR.^{103,104} An early virological response (EVR) is defined as a ≥ 2 log reduction or complete absence of serum HCV RNA at week 12 of therapy compared with the baseline level. Failure to achieve an EVR is the most accurate predictor of not achieving an SVR.^{72,105-107} Monitoring viral kinetics is thus useful for predicting whether or not an SVR is likely to develop.

Virological breakthrough refers to the reappearance of HCV RNA while still on therapy, while virological relapse is the reappearance of HCV RNA in serum after treatment is discontinued and an ETR was documented. Persons who fail to suppress serum HCV RNA by at least 2 logs after 24 weeks of therapy are null responders, while

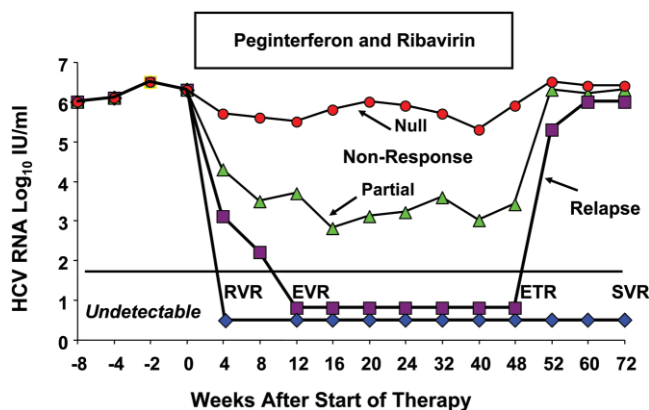


Fig. 1. Graphic display of virological responses. RVR, rapid virological response (clearance of HCV from serum by week 4 using a sensitive PCR-based assay); EVR, early virological response (≥ 2 log reduction in HCV RNA level compared to baseline HCV RNA level or HCV RNA negative at treatment week 12); SVR, sustained virological response (HCV RNA negative 24 weeks after cessation of treatment); relapse, reappearance of HCV RNA in serum after therapy is discontinued; nonresponder, failure to clear HCV RNA from serum after 24 weeks of therapy; partial nonresponder, 2 log decrease in HCV RNA but still HCV RNA positive at week 24; null nonresponder, failure to decrease HCV RNA by < 2 logs after 24 week of therapy.

those whose HCV RNA levels decrease by ≤ 2 logs IU/mL but never become undetectable are referred to as partial nonresponders.

The Optimal Treatment of Chronic HCV: Peginterferon Alfa and Ribavirin

The currently recommended therapy of chronic HCV infection is the combination of a pegylated interferon alfa and ribavirin. The choice of this regimen was based upon the results of three pivotal, randomized, clinical trials that demonstrated the superiority of this combination treatment over standard interferon alfa and ribavirin.⁷¹⁻⁷³ While not directly comparable, these three trials defined several key components of therapy, namely the appropriate dose of the drugs, the optimal duration of therapy and the need for a different regimen for patients with genotype 1 and genotype 2 and 3 infections.

There are two licensed pegylated interferons in the United States, peginterferon alfa-2b (Peg-Intron, Schering Plough Corp., Kenilworth, NJ), with a 12-kd linear polyethylene glycol (PEG) covalently linked to the standard interferon alfa-2b molecule, and peginterferon alfa-2a (Pegasys, Hoffmann-La Roche, Nutley, NJ) with a 40-kd branched PEG covalently linked to the standard interferon alfa-2a molecule.¹⁰⁸ The doses of these two forms of pegylated interferons differ.

The optimal dose of peginterferon alfa-2b, based on the original registration trial, is 1.5 $\mu\text{g}/\text{kg}/\text{week}$ dosed according to body weight (Fig. 2). Although the dose of

ribavirin used in the original registration trial was fixed at 800 mg daily, a subsequent community-based study of patients with genotype 1 infection demonstrated that weight-based ribavirin (800 mg for patients < 65 kg; 1,000 mg for patients weighing 65 to 85 kg; 1,200 mg for patients weighing 85 to 105 kg; and 1,400 mg for patients weighing > 105 kg but < 125 kg) was more effective.^{71,109}

Peginterferon alfa-2a is administered at a fixed dose of 180 $\mu\text{g}/\text{week}$ given subcutaneously together with ribavirin 1,000 to 1,200 mg daily, 1,000 mg for those who weigh ≤ 75 kg and 1,200 mg for those who weigh > 75 kg (Fig. 2).⁷² The registration trial highlighted the two beneficial effects of ribavirin, an improvement in the ETR but, more importantly, a significant decrease in the relapse rate as compared to peginterferon monotherapy treatment.

A third randomized trial determined that the optimal duration of treatment should be based on the viral genotype. The study established that patients with genotype 1 should be treated for 48 weeks with peginterferon alfa-2a plus standard weight-based ribavirin, whereas patients with genotypes 2 and 3 could be treated with peginterferon alfa-2a plus low dose ribavirin (800 mg) for 24 weeks.⁷³

For patients with HCV genotype 4 infection, combination treatment with pegylated interferon plus weight-based ribavirin administered for 48 weeks appears to be the optimal regimen, as concluded in a meta-analysis of six randomized trials.¹¹⁰ While data from another randomized trial of treatment with combination peginterferon alfa-2b plus a fixed dose of ribavirin (10.6 mg/kg per day) has suggested that 36 weeks duration of therapy is sufficient provided an EVR is achieved, these results need to be confirmed.¹¹¹

Patients with genotypes 5 and 6 are underrepresented in trials of peginterferon and ribavirin due to their limited worldwide frequency. A recent retrospective analysis of

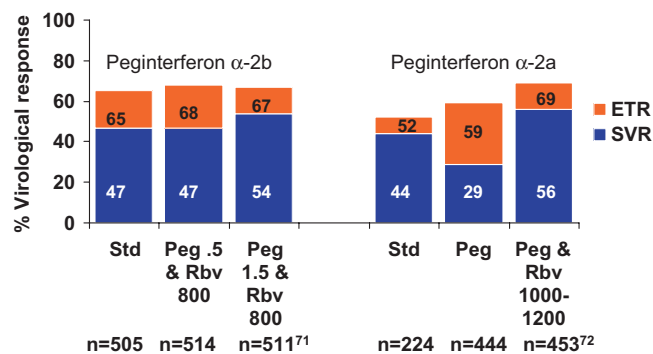


Fig. 2. Virological responses to pegylated interferon and ribavirin in the two U.S. Registration trials.^{71,72} ETR, end-of-treatment response; SVR, sustained virological response.

the treatment of patients with HCV genotype 6 concluded that treatment with peginterferon alfa plus ribavirin for 48 weeks was effective and preferable to treatment for 24 weeks.¹¹² There are insufficient data to make recommendations on the specific doses of medications or durations of treatment for persons with genotype 5 infection.

Currently, the major challenge with regard to therapy is what new approaches are needed to increase the SVR rates in (1) patients with genotype 1 infection and a high viral load; (2) HCV-infected African-American patients (see below); and (3) persons who fail to achieve an SVR using the currently approved treatment regimens.

Pretreatment Predictors of Response. Pretreatment predictors of response are useful for advising patients on their likelihood of an SVR. Absence of favorable factors should not be used, however, to deny therapy. Data on predictors of an SVR come from several sources: registration trials which have strict inclusion and exclusion criteria and may not accurately reflect the general population infected with HCV; community-based trials that may not be conducted with the same rigor as registration trials; and Veterans Affairs databases which involve men predominantly and therefore do not reflect the general population with HCV infection. Despite these caveats, multivariate analyses have identified two major predictors of an SVR among all populations studied: the viral genotype and pretreatment viral load.⁷¹⁻⁷³ Sustained virological response rates were higher in patients infected with genotype non-1 infection (mostly genotype 2 and 3) and in those with a viral load of less than 600,000 IU/mL.⁷³ Other less consistently reported baseline characteristics associated with a favorable response include the doses of peginterferon (1.5 $\mu\text{g}/\text{kg}/\text{week}$ versus 0.5 $\mu\text{g}/\text{kg}/\text{week}$) and ribavirin (>10.6 mg/kg), female gender, age less than 40 years, non-African-American race, lower body weight (≤ 75 kg), the absence of insulin resistance, elevated ALT levels (three-fold higher than the upper limit of normal), and the absence of bridging fibrosis or cirrhosis on liver biopsy.^{71,72,113}

Viral Kinetics

Measuring the rate of viral clearance from serum is helpful in predicting the likelihood of a response to therapy, for determining the optimal duration of therapy and as a stopping rule for patients with CHC. Accordingly, there has been intense interest in tailoring treatment regimens for individual patients using viral kinetics. This approach may have the benefit of limiting exposure to peginterferon and ribavirin, thus potentially leading to reduced toxicity and a cost savings.

Early Virological Response (EVR)

The absence of an EVR is the most robust means of identifying non-responders. Data from two retrospective analyses of multicenter trials indicated that failure to decrease serum HCV RNA by 2 logs or more at treatment week 12 correlated strongly with non-response in treatment-naive subjects with genotype 1 infection.^{72,105} Ninety-seven to 100% of treatment-naive patients with HCV genotype 1 infection who did not reach an EVR failed to achieve an SVR. Thus, patients who do not have an EVR can discontinue therapy early without compromising their chance to achieve an SVR. In contrast, an EVR is less accurate in predicting an SVR since only 65% to 72% of subjects who achieved an EVR ultimately attained an SVR. A completely negative test for HCV RNA at week 12 (complete EVR) is a better predictor of an SVR than a 2-log reduction in HCV RNA, 83% versus 21%.¹⁰⁵ The clinical utility of an EVR is less helpful in persons with HCV genotype 2 and 3 infection since a majority of such individuals clear virus by week 12 and respond to therapy.

Rapid Virological Response (RVR)

Earlier time points have also been examined in the hope of limiting exposure to and the side effects of therapy. Achieving an RVR is highly predictive of obtaining an SVR independent of genotype and regardless of the treatment regimen.¹⁰⁷ However, only 15% to 20% of persons with HCV genotype 1 infection and 66% with HCV genotype 2 and 3 infections achieve an RVR.^{107,114} In a retrospective analysis of the predictive value of an RVR in persons with HCV genotype 1 treated with peginterferon alfa-2a, those who achieved an RVR had an SVR rate of 91%, those who achieved a complete EVR had an SVR rate of 75%, and those who achieved an undetectable HCV RNA at week 24, had an SVR rate of 45%.¹⁰⁷

Because of the rapid clearance of virus from serum, patients who achieve an RVR may be able to shorten the duration of treatment.^{104,107} In contrast, because of a poor negative predictive value, the absence of an RVR should not be a basis for discontinuing treatment.

Utility of RVR in Patients with Genotype 1 Infection. Two analyses suggest that patients with HCV genotype 1 who achieve an RVR may be able to shorten the duration of therapy from 48 to 24 weeks. A *post hoc* analysis was conducted of a trial in which patients with chronic HCV infection were treated with peginterferon alfa-2a plus ribavirin either with a fixed dose (800 mg per day) or a weight-based dose (800-1,200 mg per day) for 24 or 48 weeks.⁷³ Overall, 24% of patients with HCV

Table 9. Summary of Studies Comparing Short Versus Standard Therapy Stratifying Based Upon RVR in Genotype 2 and 3 Patients

Trial/ Regimen	^a PegIFN α -2b 1 μ g/kg/wk & Rbv 1,000-1,200 mg daily ¹¹⁷			^b PegIFN α -2a 180 μ g/wk & Rbv 800-1,200 mg daily ¹¹⁸			^c PegIFN α -2a 180 μ g/wk & Rbv 1,00-1,200 mg daily ¹¹⁹		^d PegIFN α -2a 180 μ g/wk & Rbv 800 mg daily ¹¹⁴	
	12 ^I wks	24 ^{II} wks	24 ^{III} wks	16 ^I wks	24 ^{II} wks	24 ^{III} wks	16 wks	24 wks	16 wks	24 wks
N		283		153			150			1,469
Gt 2		76%		26%			100%			50%
Gt 3		24%		74%			0%			50%
Rx duration/ n	113	80	70	71	71	11	50	100	732	731
RVR	100	0	64	100	100	0	86	87	67	64
ETR	95	68	79	94	85	72	100	98	89	82
SVR	85	64	76	82	80	36	94	95	62	70
REL	9	6	4	13	5	50	6	3	30	13

^aPatients were randomized at baseline to a standard 24 week regimen (Group III), or a variable-duration regimen depending on results of HCV RNA testing at week 4: HCV RNA negative-treatment duration 12 weeks (Group I) or HCV RNA positive-treatment duration 24 weeks (Group II).

^bAll patients treated for 4 weeks, patients with an RVR (HCV RNA < 600 IU/ml) were randomized to 16 (Group 1) or 24 weeks (Group 2). Patients with HCV RNA \geq 600 IU/ml were treated for 24 weeks (Group 3).

^cPatients randomized 1:2 to either 16 or 24 weeks.

^dPatients randomized to 16 or 24 weeks.

Abbreviations: Gt, genotype; n, number; Rx, Treatment; REL, Relapser.

genotype 1 infection in the two 24-week treatment arms achieved an RVR. The SVR rate was 89% in patients who achieved an RVR and 19% in those who did not achieve an RVR, and was similar among those treated for 24 or 48 weeks.¹⁰⁴ Features predictive of an RVR were a low baseline viral load (\leq 200,000 IU/mL) and HCV subtype 1b.

In another study, patients with HCV genotype 1 infection and a low viral load (<600,000 IU/mL) were treated with peginterferon alfa-2b, 1.5 μ g/kg/week plus ribavirin 800 to 1,400 mg daily for 24 weeks.¹¹⁵ Overall an SVR occurred in 50% of patients.¹¹⁵ However, a sub-analysis of patients who achieved an RVR, 47%, reported an SVR rate of 89% compared to 20% among those who did not achieve an RVR. These results suggest that HCV genotype 1 patients who achieve an RVR can be successfully treated with a 24-week course of therapy.

Utility of an RVR in Persons with Genotypes 2 and 3 Infections. Four trials have evaluated the usefulness of an RVR in shortening the duration of therapy from 24 weeks to 12 to 16 weeks in patients with chronic HCV genotypes 2 and 3 infection.¹¹⁶⁻¹¹⁹ Although not directly comparable because of the use of different inclusion criteria, treatment regimens and trial designs, the data from these trials suggest that patients with genotypes 2 and 3 infection who achieve an RVR can shorten their treatment duration to 12 to 16 weeks, because the SVR rates at 12 to 16 weeks (62%-94%) were comparable to the SVR rates at 24 weeks (70%-95%), (Table 9). The one shortcoming of this approach is that the relapse rate more than doubles from 3% to 13% in those treated for 24 weeks, to 10% to 30% for those treated for 12 to 16 weeks. Importantly, patients with HCV, genotypes 2 and 3 who relapse after a short course of treatment almost always achieve an

SVR when re-treated with a standard 24-week course of therapy. No predictors of an RVR were identified in multivariate analysis in the single study that performed this analysis.¹¹⁷ Predictors of an SVR among these studies were HCV genotype 2 infection, a low baseline HCV RNA level (\leq 800,000 IU/mL), and the absence of bridging fibrosis or cirrhosis.¹¹⁸ Patients with genotype 2 and 3 infections who fail to achieve an RVR (mostly patients with HCV genotype 3 infection with high viral loads and bridging fibrosis or cirrhosis) have poor SVR rates with 24 weeks of therapy and may benefit from longer duration of treatment, but this has not been prospectively evaluated.

Based on these results, it appears that patients with HCV genotype 2 or 3 infections who achieve an RVR can shorten their duration of therapy to 12 to 16 weeks. However, a recent large multicenter, multinational trial that included 1,469 patients with genotype 2 and 3 infection has challenged this concept. Patients were randomized to receive peginterferon alfa-2a, 180 μ g / week plus 800 mg of ribavirin for either 16 or 24 weeks without stratification based upon RVR. In contrast to previous studies, the results demonstrated that treatment for 24 weeks was superior to treatment for 16 weeks (SVR rate 76% versus 65%, respectively, $P < 0.001$), even in those who achieved an RVR (85% versus 79%, respectively).¹¹⁴ One possible explanation for this varying result was that a fixed dose of ribavirin (800 mg) was used in this trial whereas weight-based ribavirin was used in the other trials.

Thus, patients with HCV genotypes 2 and 3 who are intolerant of a planned 24-week course of therapy can have their therapy discontinued between weeks 12 and 16 if they had achieved an RVR. However, patients should be informed of the higher relapse rate associated with this

strategy and be advised that re-treatment with a 24 to 48 week course of therapy may be required. Patients with HCV genotype 3 and a high viral load have lower response rates than do patients with HCV genotype 3 and a low viral load and patients with genotype 2 infections. Therefore, a longer duration of therapy should be considered for such patients. Comparable data are not available in difficult-to-treat populations such as African Americans, those with cirrhosis and those with HIV-HCV coinfection, and therefore this strategy cannot be recommended for these patient populations.

Utility of RVR in Persons with HCV Genotype 4 Infection. The role of RVR has also been assessed in patients with HCV genotype 4 infection. Patients with this genotype were treated with pegylated interferon, alfa-2b 1.5 $\mu\text{g}/\text{kg}/\text{week}$ plus ribavirin 10.6 $\text{mg}/\text{kg}/\text{day}$ for a fixed duration of 48 weeks or a variable duration based upon time to viral clearance (24 weeks if an RVR was achieved, 36 weeks if a complete EVR was achieved and 48 weeks for viral clearance beyond 12 weeks).¹¹¹ The SVR rate among those who achieved an RVR was 86%, 76% in those who achieved a complete EVR, 56% in those who had undetectable HCV RNA after 12 weeks, and 58% in those randomly assigned to 48 weeks. These results suggest that patients with HCV genotype 4 infection who achieve an RVR may be able to be treated for a shorter duration.

Effects of Higher Doses and Extended Duration of Treatment. Strategies to improve SVR rates in difficult-to-treat patients have included the use of higher doses of peginterferon and/or ribavirin or of longer durations of therapy. High dose interferon induction regimens have generally been unsuccessful. In one trial, high dose peginterferon alfa-2b induction therapy (3 $\mu\text{g}/\text{kg}$ weekly for 1 week, 1.5 $\mu\text{g}/\text{kg}/\text{weekly}$ for 3 weeks and 1 $\mu\text{g}/\text{kg}$ weekly for 44 weeks) was compared to low dose peginterferon alfa-2b (0.5 $\mu\text{g}/\text{kg}$ weekly for 48 weeks).¹²⁰ The high dose induction regimen was associated with a faster rate of viral clearance compared with the standard regimen, 22% versus 7% at week 4, but the proportion with undetectable HCV RNA was similar at the end of therapy, 71% versus 61.5%.¹²⁰ Unfortunately, SVR data were not provided.

High dose ribavirin (1,600 to 3,600 mg per day) given together with standard dose peginterferon was evaluated in a small pilot study of 10 patients with genotype 1 infection and a baseline viral load $>800,000$ IU/mL.¹²¹ Ninety percent of patients achieved an SVR. While these results are compelling, safety issues are the major concern for this approach since significant anemia developed in all patients, requiring the use of growth factors in all and blood transfusions in two patients.

The strategy of extending therapy in naive subjects with delayed virological responses, defined as clearance of HCV RNA between weeks 12 and 24, was evaluated in two studies.^{122,123} One study randomized subjects to either 48 or 72 weeks of treatment at week 12 if HCV RNA remained detectable,¹²³ and the other was a *post hoc* analysis of a study in which randomization of treatment duration occurred at baseline.¹²² The study populations were not homogeneous, differing in their baseline characteristics and the regimens utilized were different. Nevertheless, the results showed a trend toward a higher SVR rate by extending therapy from 48 to 72 weeks. The SVR rate increased from 18% for 48 weeks treatment to 38% for 72 weeks of treatment in one study¹²³ and 17% to 29% in the other study.¹²² The increased SVR was primarily due a lower relapse rate in the patients treated for 72 weeks. An additional study demonstrated that patients who failed to achieve an RVR (HCV RNA detectable at treatment week 4) also seemed to benefit from extending therapy from 48 to 72 weeks.¹²⁴ The SVR rates were significantly higher in patients who received treatment for 72 (45%) compared to those treated for 48 weeks (32%).¹²⁴ It is clear that not all patients will benefit from extended therapy judging from the results of the trial in which randomization to 48 or 72 weeks of therapy occurred at baseline.¹²² No difference in SVR rates was observed between those treated for 48 compared to 72 weeks (53% versus 54%, respectively).¹²² Thus, prolonging therapy can be considered in patients who are slow to respond (clearance of HCV RNA between weeks 12 and 24). Further studies are needed to determine whether extended therapy would be beneficial to patients who fail to clear virus between weeks 4 and 12.

Adverse Events. Almost all patients treated with peginterferon and ribavirin experience one or more adverse events during the course of therapy. Adverse events are a major reason that patients decline or stop therapy altogether. In the registration trials of peginterferon alfa-2a and 2b plus ribavirin, 10% to 14% of patients had to discontinue therapy due to an adverse event.^{71,72} The most common adverse events in these trials were influenza-like side effects such as fatigue, headache, fever and rigors, which occurred in more than half of the patients, and psychiatric side effects (depression, irritability, and insomnia), which occurred in 22% to 31% of patients.

Laboratory abnormalities are the most common reasons for dose reduction. Among these, neutropenia (absolute neutrophil count [ANC] of 1500 mm^3) was a frequent laboratory abnormality, occurring in 18% to 20% in the two large phase III clinical trials where the dose was reduced 50% for an ANC of 750 mm^3 and permanently discontinued for an ANC of <500

mm^3 .^{71,72} Severe neutropenia, $\text{ANC} < 500 \text{ mm}^3$, occurred in 4% of subjects. Despite the decline in the neutrophil count, serious infections are uncommon¹²⁵ and granulocyte colony stimulating factor is rarely necessary except in patients with advanced cirrhosis. Anemia was observed in approximately one-third of patients, reaching a nadir within 6 to 8 weeks. Dose modification for anemia (hemoglobin level $< 10 \text{ g/dL}$) was required in 9% to 15% in the two phase III registration trials. Growth factors, such as erythropoietin and darbepoietin, have been used to counter the anemia associated with peginterferon and ribavirin. Although growth factors improve a patient's sense of well-being and have reduced the requirement for ribavirin dose reduction, their use has not been shown to improve SVR rates.¹²⁶⁻¹²⁸ In one analysis, the use of a hematological growth factor nearly doubled the cost of treatment for chronic hepatitis C.¹²⁹ Although generally safe, erythropoietin and darbepoietin use has been associated with serious side effects including cardiovascular and thromboembolic events, pure red cell aplasia, progression of certain cancers, and death.¹³⁰

There has also been a report of a new, orally active thrombopoietin-receptor agonist, called eltrombopag that stimulates thrombopoiesis.¹³¹ Given for 12 weeks, it allowed successful therapy of HCV patients who had baseline thrombocytopenia (20,000 to 70,000 mm^3), but whether this product will permit patients to complete a full course of therapy has yet to be evaluated. Therefore, routine use of growth factors cannot be recommended at this time and dose reduction is the primary mode for managing cytopenias.

Neuropsychiatric side effects include depression, anxiety, insomnia, emotional lability, mood disorders, frank psychosis, suicidal ideation, actual suicide, and homicide. The most consistent risk factors for developing depression are the presence of mood and anxiety symptoms prior to therapy. A past history of depression and of receiving higher doses of interferon, as well as being female, have been identified as risk factors, but are less reliable ones.¹³²

Interferon-induced depression appears to be composed of two overlapping syndromes — a depression-specific syndrome characterized by mood, anxiety, and cognitive complaints, and neurovegetative symptoms, characterized by fatigue, anorexia, pain and psychomotor slowing.¹³³⁻¹³⁵ Depression-specific symptoms are highly responsive to serotonergic antidepressants whereas neurovegetative symptoms are not. These symptoms may be more effectively treated with agents that modulate catecholaminergic function. When selecting an agent, consideration should be given to drug-drug interactions, underlying hepatic function, the possibility of drug-induced hepatotoxicity and other adverse side effects. Con-

sultation and follow up with a psychiatrist is advised (see section on Management of Psychiatric Illness).

Pegylated interferon may induce autoimmune disorders, such as autoimmune thyroiditis, or may worsen pre-existing autoimmune disorders. Therefore, the presence of autoimmune conditions prior to treatment is a relative contraindication to therapy. A major dilemma, however, is that chronic HCV infection may present with features that simulate idiopathic autoimmune hepatitis, including the presence of a positive test for antinuclear antibodies. This poses the problem of distinguishing between chronic HCV infection with autoimmune features, for which treatment with antiviral therapy is appropriate, and persons with non-hepatitis C-related autoimmune hepatitis with superimposed chronic HCV infection which requires treatment with immunosuppressive drugs. A helpful distinction is a prior history of autoimmune hepatitis, the presence of other autoimmune conditions and the identification of specific HLA characteristics (See AASLD guidelines for Autoimmune Hepatitis).¹³⁶ A liver biopsy may also be helpful. An individualized approach with careful monitoring is recommended if treatment is initiated.

With regard to ribavirin, the most common side effect is hemolytic anemia. Since ribavirin is cleared by the kidney, the drug should be used with extreme caution in patients with renal disease and renal failure. Other side effects associated with ribavirin include mild lymphopenia, hyperuricemia, itching, rash, cough and nasal stuffiness. Ribavirin is reported to cause fetal death and fetal abnormalities in animals and thus it is imperative for persons who receive the drug to use strict contraceptive methods both during treatment and for a period of 6 months thereafter. The education of patients and caregivers about side effects and their management is an integral component of treatment and is important for a successful outcome.

Selection of Patients for Treatment. Current recommendations for treatment of persons with chronic HCV infection derive from data collected in the randomized registration trials. However these trials have usually been restrictive in their exclusion criteria and thus have not reflected the general population who require therapy. More data are needed in certain groups such as those with renal disease, depression and active substance abuse, children, and those with HIV/HCV co-infection. As with all decisions in medicine, a balance must be struck between the benefit and risk related to therapy. Application of these principles can be challenging and the relative strength of a recommendation will need to vary accordingly (Tables 10, 11 and 12).

Table 10. Characteristics of Persons for Whom Therapy Is Widely Accepted

- Age 18 years or older, and
- HCV RNA positive in serum, and
- Liver biopsy showing chronic hepatitis with significant fibrosis (bridging fibrosis or higher), and
- Compensated liver disease (total serum bilirubin <1.5 g/dL; INR 1.5; serum albumin >3.4, platelet count 75,000/mm³ and no evidence of hepatic decompensation (hepatic encephalopathy or ascites), and
- Acceptable hematological and biochemical indices (Hemoglobin 13 g/dL for men and 12 g/dL for women; neutrophil count 1500/mm³ and serum creatinine <1.5 mg/dL, and
- Willing to be treated and to adhere to treatment requirements, and
- No contraindications (Table 12)

It must be re-emphasized that the recommendations on the selection of patients for treatment are guidelines and not fixed rules; management and treatment considerations should be made on a case-by-case basis, taking into consideration the experience of the practitioner together with the acceptance of risk by the patient.

Assessment Prior to Treatment and Monitoring During and After Therapy

It is advisable to assess the risk of underlying coronary heart disease, to control preexisting medical problems, such as uncontrolled diabetes and hypertension, and to pre-screen all candidates for symptoms of depression prior to initiating therapy. A number of validated self-rated or clinician-rated scales to assess depression are available.¹³⁷⁻¹⁴⁰

Patients should be monitored during therapy to assess the response to treatment and for the occurrence of side effects. A reasonable schedule would be monthly visits during the first 12 weeks of treatment followed by visits at 8 to 12 week intervals thereafter until the end of therapy. At each visit the patient should be questioned regarding the presence of side effects and depression. They should also be queried about adherence to treatment. Laboratory

Table 11. Characteristics of Persons for Whom Therapy Should Be Individualized

- Failed prior treatment (non-responder and relapsers) either interferon with or without ribavirin or peginterferon monotherapy
- Current users of illicit drugs or alcohol but willing to participate in a substance abuse program (such as a methadone program) or alcohol support program.
- Liver biopsy evidence of either no or mild fibrosis
- Acute hepatitis C
- Coinfection with HIV
- Under 18 years of age
- Chronic renal disease (either requiring or not requiring hemodialysis)
- Decompensated cirrhosis
- Liver transplant recipients

Table 12. Characteristics of Persons for Whom Therapy Is Currently Contraindicated

- Major uncontrolled depressive illness
- Solid organ transplant (renal, heart, or lung)
- Autoimmune hepatitis or other autoimmune condition known to be exacerbated by peginterferon and ribavirin
- Untreated thyroid disease
- Pregnant or unwilling to comply with adequate contraception
- Severe concurrent medical disease such as severe hypertension, heart failure, significant coronary heart disease, poorly controlled diabetes, chronic obstructive pulmonary disease
- Age less than 2 years
- Known hypersensitivity to drugs used to treat HCV

monitoring should include measurement of the complete blood count, serum creatinine and ALT levels, and HCV RNA by a sensitive assay at weeks 4, 12, 24, 4 to 12 week intervals thereafter, the end of treatment, and 24 weeks after stopping treatment. Thyroid function should be monitored every 12 weeks while on treatment.

Patients who achieve an SVR usually have improvement in liver histology and clinical outcomes.^{141,142} However, patients who achieve an SVR but who have cirrhosis are at risk for hepatic decompensation and HCC and death in the short term (5 years),¹⁴³ and therefore should continue to be monitored periodically, including screening for HCC (See AASLD guidelines on Management of Hepatocellular Carcinoma).¹⁴⁴ There is no role for a post-treatment liver biopsy among those who achieve an SVR.

Recommendations

9. Treatment decisions should be individualized based on the severity of liver disease, the potential for serious side effects, the likelihood of treatment response, the presence of comorbid conditions, and the patient's readiness for treatment (Class IIa, Level C).

10. For patients in whom liver histology is available, treatment is indicated in those with bridging fibrosis or compensated cirrhosis provided they do not have contraindications to therapy (Class I, Level B).

11. The optimal therapy for chronic HCV infection is the combination of peginterferon alfa and ribavirin (Class I, Level A).

12. HCV RNA should be tested by a highly sensitive quantitative assay at the initiation of or shortly before treatment and at week 12 of therapy, (Class I, Level A).

Genotypes 1 and 4 HCV Infection

13. Treatment with peginterferon plus ribavirin should be planned for 48 weeks; the dose for peginterferon alfa-2a is 180 μg subcutaneously per week together with ribavirin using doses of 1,000 mg for those ≤75 kg in weight and 1,200 mg for those >75 kg; the

dose for peginterferon alfa-2b is 1.5 µg/kg subcutaneously per week together with ribavirin using doses of 800 mg for those weighing < 65 kg, 1,000 mg for those weighing > 65 kg to 85 kg, 1,200 mg for > 85 kg to 105 kg, and 1,400 mg for > 105 kg (Class I, Level A).

14. Treatment may be discontinued in patients who do not achieve an early virological response (EVR; ≥ 2 log reduction in HCV RNA at week 12 of treatment) (Class I, Level A).

15. Patients who do not achieve a complete EVR (undetectable HCV RNA at week 12 of treatment) should be re-tested at week 24, and if HCV RNA remains positive, treatment should be discontinued (Class I, Level A).

16. For patients with genotype 1 infection who have delayed virus clearance (HCV RNA test becomes negative between weeks 12 and 24), consideration should be given to extending therapy to 72 weeks (Class IIa, Level B).

17. Patients with genotype 1 infection whose treatment continues through 48 to 72 weeks and whose measurement of HCV RNA with a highly sensitive assay is negative at the end of treatment should be retested for HCV RNA 24 weeks later to evaluate for a sustained virological response (SVR; HCV RNA negative 24 weeks after cessation of treatment) (Class I, Level A).

Genotype 2 or Genotype 3 HCV Infection

18. Treatment with peginterferon plus ribavirin should be administered for 24 weeks, using a ribavirin dose of 800 mg (Class I, Level A).

19. Patients whose treatment continues through 24 weeks and whose measurement of HCV RNA with a highly sensitive assay is negative should be retested for HCV RNA 24 weeks later to evaluate for an SVR (Class I, Level A).

20. Patients with HCV-related cirrhosis who achieve an SVR, regardless of the genotype, should continue to be monitored at 6 to 12 month intervals for the development of HCC (Class IIa, Level C).

Retreatment of Persons Who Failed to Respond to Previous Treatment

The approach to patients who fail therapy depends on the nature of the initial response, on the potency of initial treatment and on host-viral factors. Twenty to fifty percent of patients treated with pegylated interferon and ribavirin will not achieve an SVR. Failure to achieve an SVR with a course of pegylated interferon and ribavirin can be a consequence of non-response, virological breakthrough, or relapse. Poor adherence to the prescribed treatment and inappropriate dose reductions can contrib-

ute to poor response rates. The induction of antibodies to peginterferon accounts for only a minority of cases.

Non-Responders. Approximately thirty percent of patients treated with pegylated interferon and ribavirin are unable to clear virus from the serum.^{71,72} Options for non-responders to pegylated interferon and ribavirin are limited. Retreatment with the same regimen leads to an SVR in fewer than 5% of patients and therefore cannot be recommended.¹⁴⁵ There is no convincing evidence that switching to alternative interferons is effective.¹⁴⁶ Maintenance therapy with peginterferon with the goal of delaying or preventing progression to cirrhosis and/or hepatic decompensation is currently being assessed in two ongoing and one completed randomized trials in the U.S. and Europe.¹⁴⁷ Results of one of them, the HALT-C trial, have recently been reported.¹⁴⁸ In this trial, although serum ALT levels, HCV RNA and hepatic necroinflammation were statistically significantly reduced in the treated arm, the rates of clinical decompensation and progression to histologic cirrhosis were similar in both the treated and untreated groups, 34.1% and 33.8%, respectively (hazard ratio 1.01). Thus, based on the results of the HALT-C Trial, maintenance low dose peginterferon alfa-2a, 90 µg per week, is not indicated in patients with hepatitis C who have bridging fibrosis or cirrhosis and who have not responded to a standard course of peginterferon and ribavirin therapy. Until data become available from retreatment studies using alternate regimens, the decision to undergo retreatment should be individualized. Non-responders to peginterferon and ribavirin with advanced fibrosis should follow AASLD guidelines for screening for HCC and varices and be evaluated for liver transplantation if they are appropriate candidates. Patients with mild fibrosis (Metavir and IASL ≤ 1 or and Batts-Ludwig and Ishak ≤ 2) should be monitored without treatment.

For non-responders to standard interferon either with or without ribavirin, retreatment with peginterferon alfa-2a or 2b has been evaluated in three trials.¹⁴⁹⁻¹⁵¹ The SVR rates were higher among patients who had previously received interferon monotherapy, ranging from 20% to 40%, and were lower among non-responders to the combination of interferon and ribavirin, ranging from 8% to 10%. Persons more likely to achieve an SVR from retreatment included those with genotype non-1 infection, who had lower baseline HCV RNA levels, who had lesser fibrosis, who were of the Caucasian race, and whose prior treatment had consisted of interferon monotherapy.¹⁵⁰

Relapsers. In the majority of instances, virological relapse occurs within the first 12 weeks and late relapse, beyond 24 weeks, is extremely uncommon. Patients with virological relapse are likely to respond to the same regi-

men given a second time but will still experience an unacceptable rate of relapse. For relapsers to standard interferon and ribavirin, two regimens have been evaluated — high dose peginterferon alfa-2b, 1.5 $\mu\text{g}/\text{kg}/\text{week}$ with fixed dose ribavirin 800 mg daily, and low dose peginterferon alfa-2b, 1 $\mu\text{g}/\text{kg}/\text{week}$ plus weight-based ribavirin, 1,000 to 1,200 mg daily.¹⁵¹ The overall SVR rate was 42% and, although it was higher in the group treated with the higher dose of peginterferon (50%) than in those treated with the lower dose (32%), the number of treated patients was too few to draw meaningful conclusions. Data on retreatment of relapsers to peginterferon and ribavirin have not been published.

Recommendations

21. Retreatment with peginterferon plus ribavirin in patients who did not achieve an SVR after a prior full course of peginterferon plus ribavirin is not recommended, even if a different type of peginterferon is administered (for relapsers, Class III, Level C; for non-responders, Class III, Level B).

22. Retreatment with peginterferon plus ribavirin can be considered for non-responders or relapsers who have previously been treated with non-pegylated interferon with or without ribavirin, or with peginterferon monotherapy, particularly if they have bridging fibrosis or cirrhosis (Class IIa, Level B).

23. Maintenance therapy is not recommended for patients with bridging fibrosis or cirrhosis who have failed a prior course of peginterferon and ribavirin (Class III, Level B).

Special Patient Groups

Treatment of Persons with Normal Serum Aminotransferase Values. In the past, there has been uncertainty about how to manage persons infected with HCV who have *normal* aminotransferase levels, specifically the serum ALT.^{152,153} One issue has been the question of what constitutes a normal ALT value; another had been whether or not persons with a normal ALT warrant treatment.

Regarding the former, the upper limit of normal (ULN) is generally established in individual laboratories by screening presumably healthy volunteers and defining a mean value ± 2 standard deviations. Not usually accounted for, however, is that the ALT value differs by age, race, and gender, and by body mass index.^{154,155} Taking these items into consideration, it has recently been suggested that the ULN for ALT should in fact be 30 IU/L for men and 19 IU/L for women,¹⁵⁶ but many laboratories continue to set the ULN of ALT at about 40 IU/L.

Therefore, since ALT values can fluctuate over time, a common definition for the existence of persistently normal aminotransferase levels is the identification of an ALT value of less than 40 IU/L on 2 to 3 occasions separated by at least a month over a period of six months.^{156,157}

While on average, persons with persistently normal ALT values have significantly less liver fibrosis than persons whose ALT levels are abnormal,^{78,155,158,159} there are reports of marked fibrosis (5%-30%) and even cirrhosis (1.3%) in persons with normal ALT values.¹⁶⁰⁻¹⁶² Thus, it is evident that HCV-infected persons with normal ALT values do warrant treatment if the liver biopsy shows significant fibrosis. Moreover, there are multiple studies that report SVR rates with standard-of-care treatment that do not differ from those achieved in persons with abnormal enzymes, and that treatment is equally as safe.^{82-84,163-165}

Recommendations

24. Regardless of the serum alanine aminotransferase level, the decision to initiate therapy with pegylated interferon and ribavirin should be individualized based on the severity of liver disease by liver biopsy, the potential for serious side effects, the likelihood of response, and the presence of comorbid conditions (Class I, Level B).

25. The treatment regimen for HCV-infected persons with normal aminotransferase levels should be the same as that used for persons with elevated serum aminotransferase levels (Class I, Level B).

Diagnosis and Treatment of HCV-Infected Children. The exact prevalence of HCV infection among children in the U.S. is uncertain.¹⁶ Recent national census results indicate that there are between 23,048 and 42,296 children in the U.S. who have chronic HCV infection with 7,200 new cases occurring yearly, most resulting from vertical transmission.¹⁶⁶ The seroprevalence increases with age: 0.2% of children 6 to 11 years and 0.4% of children aged 12 to 19 years have positive HCV antibodies.¹⁶⁷ A subsequent study has reported a lower incidence of HCV infection (0.1%) among an urban population of HIV-negative children under the age of 6 years.¹⁶⁸

Because of universal testing of blood donors for anti-HCV since 1992,^{169,170} mother-to-child (vertical or perinatal) transmission has replaced transfusion-associated hepatitis C to become the most common mode of HCV transmission among children in the U.S. The prevalence of HCV infection among women of child-bearing age is 1.2%, and is higher in women who are injection drug users or who are HIV-coinfected.^{167,171,172} However, routine screening of all pregnant women for HCV antibodies

is not recommended.¹⁶⁷ Selective testing based on high risk has been advocated by some, but does not detect all cases of HCV infection.¹⁶⁷

The risk of perinatal HCV transmission is 4% to 6%, and is 2- to 3-fold higher for mothers with HIV/HCV co-infection.¹⁷³⁻¹⁸⁰ Some pediatricians advise against the use of fetal scalp monitors and recommend delivery within 6 hours of rupture of membranes to avoid transmission when the mother is known to be HCV-infected.^{17,181} Data supporting delivery of HCV-infected mothers by cesarean section is scant and most authorities do not recommend this approach.¹⁶⁷ Similarly, although HCV has been identified in breast milk of infected mothers,¹⁸² there are no data to show that HCV is transmitted in breast milk; therefore breastfeeding is not prohibited in HCV-infected mothers.¹⁸³ Finally, in the U.S., horizontal transmission from child to child is rare. Therefore, the American Academy of Pediatrics does not recommend restricting children with chronic HCV infection from school attendance or participation in routine activities, including sports.¹⁶⁷

Testing of infants born to HCV infected women should be preformed because of the risk of perinatal transmission. When to test can be challenging because maternal antibodies passively transferred to the newborn may persist for up to 18 months of age.^{17,184} Therefore, current recommendations advocate postponing anti-HCV testing in exposed infants until 18 months of age.¹⁶⁷ If earlier diagnosis is desired, testing for HCV RNA may be performed at or after the infant's first well-child visit at 1 to 2 months of age. However, the sensitivity of HCV RNA testing at this time is low and a negative test should be repeated at a later date. Therefore it may be more prudent to defer HCV RNA testing until 6 months when sensitivity of the test is improved.¹⁸⁵

There are several features of HCV infection that differ between children and adults. Children who are acutely infected with HCV, like adults, are generally asymptomatic, but they are more likely than infected adults to spontaneously clear the virus and are more likely to have normal ALT levels.¹⁸⁶ In a recent report of 157 children with HCV infection identified between 1990 and 2001, 28% cleared infection after 10 years of follow up.¹⁸⁷ Among neonatal cases, 25% had spontaneous clearance by 7.3 years. Younger age at follow up and a normal ALT value both favored spontaneous clearance ($P < 0.0001$).¹⁸⁷

Children with chronic HCV infection, irrespective of mode of acquisition (vertical versus transfusion), have been shown to have minimal progression of their disease over 5 to 20 years.¹⁸⁸⁻¹⁹¹ Biopsy studies in children generally have demonstrated minimal fibrosis and rare cirrho-

sis 15 to 20 years after infection.¹⁹²⁻¹⁹⁴ Nevertheless, significant disease can occur as reported in a study of 60 children, 12% of whom had bridging fibrosis on liver biopsy after a mean duration of infection of 13 years.¹⁹⁵ On follow up, two patients underwent liver transplantation, one of whom had an undiagnosed HCC.

To date, little is known about the potential for significant liver-related morbidity and mortality over the lifetime of the child. In one retrospective study of elderly Asian patients infected with HCV as children, 71% of those infected for greater than 60 years had cirrhosis on liver biopsy.¹⁹² Unfortunately, no information was available regarding the presence of mitigating factors such as non-alcoholic fatty liver disease (NAFLD), diabetes, alcohol abuse or other viral hepatitis in these patients.

As with adults, the biggest challenge is identifying appropriate candidates for therapy. It may be concluded that the relatively mild disease experienced by most children early in the course of infection and the likelihood of improved future treatments argues against routine treatment. However, it is equally reasonable to accept that the average child is likely to be infected in excess of 50 years and therefore, routine treatment may still be warranted.

Early studies of therapy in children were restricted to interferon monotherapy because animal studies had suggested ribavirin was potentially teratogenic and embryocidal in humans.¹⁹⁶⁻²⁰¹ The addition of ribavirin to interferon alfa resulted in higher SVR rates compared to interferon monotherapy.^{199,200} Since pegylated interferon alfa together with ribavirin have become the standard of care for the treatment of HCV infection in adults, most recent studies of treatment of HCV-infected children have involved the use of pegylated interferon alfa together with ribavirin. In one such study, 59% of 62 infected children and adolescents treated with pegylated interferon alfa-2b, 1.5 $\mu\text{g}/\text{kg}$ body weight once weekly together with ribavirin, 15 mg/kg per day for 48 weeks, achieved an SVR.²⁰² As with adults, the SVR rates were significantly higher in those children with genotypes 2 or 3 infections (100%) compared to those with infection due to genotype 1 (48%) on a per-protocol analysis. Adverse events led to dose modification in 31% and dose discontinuation in 7%. Similar results were obtained in a subsequent study documenting an overall SVR rate of 50%, 23% of whom required interferon dose reduction for neutropenia.²⁰³

Recent data indicate that treatment of HCV-infected children with peginterferon and ribavirin is safe and leads to SVR rates that are superior to those of standard interferon. Accordingly, the combination of peginterferon alfa-2b and ribavirin has been approved by the FDA for the treatment of children. The effectiveness of treating children with genotype 1 infection for 48 weeks using

Table 13. Four Pivotal Studies of Treatment of Chronic Hepatitis C in HIV-Infected Persons

Characteristic	APRICOT ²¹⁷	ACTG 5071 ²¹⁶	RIBAVIC ²¹⁸	Barcelona ²¹⁵
Number enrolled	868	133	412	95
Peginterferon	2a	2a	2b	2b
Ribavirin	800 mg	600 up to 1g	800 mg	0.8 g, 1 g, 1.2 g ¹
HIV and CD4+ status	>200/mm ³ or 100-200/mm ³ and HIV RNA < 5000 c/mL	>100/mm ³ and HIV RNA < 10,000 c/mL	>200/mm ³	>250/mm ³ and HIV RNA < 10,000 c/mL
ALT	"Elevated" twice	NA	NA	1.5 ULN
% Genotype 1 ²	60	77	48	55
% bridging fibrosis or cirrhosis ²	12	11 (cirrhosis)	39	29
Genotype 1 peg-RBV SVR rate ³	29%	14%	17%	38%

Abbreviations: ALT, alanine aminotransferase; ULN, upper limit of normal; c/mL, copies/mL; NA, not applicable. Table adapted from Thomas, HEPATOLOGY 2006;43:S221-S229.

¹Based on body weight <65, 65-75, >75 kg.

²Taken from peginterferon and ribavirin arm; cirrhosis defined as F4-6 MHA1 or F3-4 Metavir and Scheurer.

³Refers to the sustained virologic response (SVR) rate for HIV-infected persons taking peginterferon and ribavirin. Rates are for patients with genotype 1 hcv infection except for the RIBAVIC and Barcelona studies that grouped genotypes 1 and 4.

both drugs appears substantiated, but current data are insufficient to recommend using a 24 week course of treatment in children with genotype 2 or 3 infection.

Recommendation:

26. The diagnosis and testing of children suspected of being infected with HCV should proceed as for adults (Class I, Level B).

27. Routine testing for anti-HCV at birth of children born to HCV-infected mothers is not recommended because of the high rate of positive antibody due to passive transfer from the mother. Testing for anti-HCV may be performed at 18 months of age or older (Class I, Level B).

28. Testing for HCV RNA may be considered at 1-2 months of age in infants born to HCV-infected mothers if early diagnosis is desired (Class II, Level B).

29. Children aged 2-17 years who are infected with HCV should be considered appropriate candidates for treatment using the same criteria as that used for adults. (Class IIa, Level B).

30. Children should be treated with pegylated interferon alfa-2b, 60 µg/m² weekly in combination with ribavirin, 15 mg/kg daily for a duration of 48 weeks (Class I, Level B).

Diagnosis, Natural History, and Treatment of Persons with HIV Coinfection. Approximately 25% of HIV-infected persons in the Western world have chronic HCV infection.²⁰⁴ In the United States, up to 8% of those with chronic HCV infection may be HIV coinfecting.^{7,204,205} Since the advent of highly active antiretroviral therapy (HAART) in 1996, HCV-related liver

disease has become an increasingly important cause of morbidity and mortality in HIV-infected persons.²⁰⁵⁻²⁰⁷

Because of the high prevalence of HIV/HCV coinfection, and because the management of each infection can differ in dually-infected persons, all HIV-infected persons should be tested for HCV and all HCV-infected persons with HIV risk factors should be tested for HIV. As in HIV-uninfected persons, the usual approach is to first test for anti-HCV and to confirm the positive results with a highly sensitive assay. However, approximately 6% of HIV-positive persons fail to develop HCV antibodies; therefore, HCV RNA should be assessed in HIV-positive persons with unexplained liver disease who are anti-HCV negative.^{208,209}

The urgency for treatment of persons who are co-infected is greater than it is in those with HCV infection alone. Progression of liver disease is more rapid in HIV/HCV-co-infected persons, in whom there is an approximately twofold increased risk of cirrhosis.^{210,211} Successful treatment of HCV also might improve the tolerability of HAART by reducing the risk of hepatotoxicity.^{212,213}

The likelihood of achieving an SVR is lower in HIV/HCV co-infected persons than in those with HCV monoinfection.²¹⁴⁻²¹⁸ The reduced SVR likelihood appears to be due in part to higher HCV RNA levels in HIV-infected persons compared to those with just HCV infection.

The combined use of peginterferon alfa and ribavirin is approved by the FDA for treatment of hepatitis C in HIV-infected persons. The superiority of peginterferon alfa and ribavirin treatment has been shown in four large studies (Table 13).²¹⁶⁻²¹⁹ In the largest study (APRICOT), 868 persons were randomized to receive either

standard interferon alfa-2a (3 mU tiw) plus ribavirin (800 mg daily), peginterferon alfa-2a 180 μ g per week plus placebo, or peginterferon alfa-2a, 180 μ g weekly plus ribavirin 800 mg daily for 48 weeks; the overall SVR rates were 12%, 20%, and 40%, respectively.²¹⁷ For persons with genotype 1 infection, the SVR rate was 29% with peginterferon alfa and ribavirin, whereas an SVR was observed in 62% of those with genotype 2 or 3 infections. In addition to genotype, lower pretreatment HCV RNA levels (equivalent to $\leq 5.7 \log_{10}$ IU/mL) were also associated with achieving an SVR. As in persons without HIV infection, those who took peginterferon alfa and ribavirin, but did not achieve an EVR (85 of 289), rarely attained an SVR (2 of 85). Medication was discontinued in 25% of those taking peginterferon alfa and ribavirin; in 15%, discontinuation was due to adverse events. Hepatic decompensation occurred in 14 of the 860 patients who received at least one dose of study medication. Each of the 14 subjects had cirrhosis and 7 subjects had Child-Turcotte-Pugh (CTP) scores of 7 or higher at baseline; also associated with decompensation were other markers of cirrhosis, such as low platelet counts, and didanosine use.²²⁰ In general, similar response rates and toxicity were observed in the other three large studies including the two conducted with peginterferon alfa 2b.

Data on which to base definitive recommendations on the doses and duration of therapy for co-infected patients do not exist. Until such data become available, 48 weeks of ribavirin and peginterferon at doses used for HCV-monoinfected patients is recommended.

There are additional safety concerns in the treatment of HIV/HCV co-infected patients. Ribavirin-associated anemia is a greater problem in persons co-infected with HIV than in those with monoinfection.²²¹ Ribavirin-related anemia is especially common and severe in persons taking AZT.²²² Ribavirin inhibits inosine-5-monophosphate dehydrogenase, an effect that potentiates didanosine (ddI) toxicity.^{223,224} Since symptomatic and even fatal lactic acidosis has been reported in some co-infected persons receiving ribavirin and ddI, ribavirin should not be used in persons receiving this drug.^{220,224-226} Interferon alfa therapy causes a dose-related reduction in the white blood cell count and the absolute CD4 lymphocyte count, but the percentage of CD4 cells remains essentially unchanged, and its use is not associated with the development of opportunistic infections.^{216-218,221,227-230} In fact, during therapy, peginterferon alfa use is associated with an approximately 0.7-log reduction in HIV RNA levels, suggesting a potential direct beneficial effect on HIV replication, although this effect is not sustained after peginterferon alfa is discontinued.

There continues to be controversy as to which HIV/HCV co-infected patients should undergo anti-HCV treatment since the greater risk of cirrhosis must be weighed against lower SVR rates and additional safety concerns. As is the case for HIV-uninfected patients, these decisions are influenced by the stage of liver disease, (see section on liver biopsy). In HIV/HCV co-infected persons newly initiating antiretroviral therapy, there is insufficient information to recommend a particular waiting period before commencing HCV treatment. In addition, there are very limited data on SVR rates in persons with CD4+ lymphocyte counts below 200/mm³ and it is not clear which is more informative, the CD4+ lymphocyte nadir or the CD4+ count at the time that HCV therapy is started.^{231,232} Most authorities wait at least several months before initiating therapy so that the adverse effects of the antiretroviral therapy are not confused with those caused by peginterferon or ribavirin. If indicated, HIV treatment should be optimized before providing HCV treatment. For HIV/HCV co-infected patients who do not meet one of the established criteria for HIV treatment (e.g., CD4+ lymphocyte count $> 350/\text{mm}^3$), it is controversial whether antiretroviral therapy provides any advantage, either to improve the likelihood of SVR or to delay progression of HCV. Patients with decompensated liver disease (CTP class B or C) are not treatment candidates and should be considered for liver transplantation.

Outcomes with liver transplantation for patients who are HIV-infected are under evaluation.²³³ Patients who are HIV/HCV coinfecting appear to have more rapid progression of liver fibrosis and cirrhosis than those infected with just HCV alone. In addition, both drug interaction and mitochondrial toxicity were problematic issues.²³⁴

Recommendations

31. Anti-HCV testing should be performed in all HIV-infected persons (Class I, Level B).

32. 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 (Class I, Level B).

33. Hepatitis C should be treated in the HIV/HCV co-infected patient 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 (Class I, Level A).

34. Initial treatment of hepatitis C in most HIV-infected patients should be peginterferon alfa plus ribavirin for 48 weeks at doses recommended for HCV mono-infected patients (see recommendation 13) (Class I, Level A).

35. When possible, patients receiving zidovudine (AZT) and especially didanosine (ddI) should be switched to an equivalent antiretroviral agent before beginning therapy with ribavirin (Class I, Level C).

36. HIV-infected patients with decompensated liver disease (CTP Class B or C) should not be treated with peginterferon alfa and ribavirin and may be candidates for liver transplantation (Class IIa, Level C).

Treatment of Patients with Kidney Disease. Hepatitis C affects the kidney in at least two ways. First, patients with chronic kidney disease (CKD) who undergo hemodialysis are at high risk of acquiring HCV infection,²³⁵⁻²³⁷ the risk increasing the longer the patient is on hemodialysis.²³⁶ Data from 8,615 patients in hemodialysis units screened for HCV in seven countries revealed the presence of the virus in a mean of 13.5%, ranging from 2.6% in the United Kingdom to 22.9% in Spain; the rate in U.S. units was 14.9%.²³⁵ Even higher rates have been reported from dialysis units in some developing countries.^{238,239} A national survey in U.S. dialysis centers in the year 2000 found anti-HCV to be present in 8.4% of patients and in 1.7% of staff.²³⁷ This high rate of HCV transmission is due to direct percutaneous exposure to infectious blood because of inadequate infection control.²⁴⁰ Its source is cross-contamination between patients because of lack of disinfection of commonly utilized medication equipment and supplies, the use of shared vials of heparin, and blood spills not immediately cleaned. Curbing transmission thus requires strict adherence to infection control measures together with monitoring of HCV-negative patients. If these principles are adhered to, there is no need to isolate HCV-positive patients or even to dialyze them separately on a dedicated machine.²⁴⁰⁻²⁴²

Second, infection with HCV may be associated with the development of a number of extrahepatic disorders, one of the most serious being essential mixed (type II) cryoglobulinemia.²⁴³⁻²⁴⁶ Its cardinal feature is a systemic vasculitis, presenting clinically as palpable purpura, arthralgias and arthritis, fatigue, peripheral neuropathy, and glomerulonephritis.²⁴³⁻²⁴⁶ The most common histologic patterns are diffuse membrano-proliferative glomerulonephritis,²⁴⁶ and less commonly, non-cryoglobulinemic membrano-proliferative glomerulonephritis, focal and segmental glomerulosclerosis, and fibrillary and immunactoid glomerulopathies.²⁴³⁻²⁴⁸ The majority of persons with essential mixed cryoglobulinemia are infected with HCV. Since the early presentation of cryoglobulinemia may consist simply of proteinuria and renal dysfunction without symptoms of either cryoglobulinemia or liver disease, all persons with proteinuria and cryoglobulinemia

should be screened for HCV RNA even if they lack clinical and/or biochemical evidence of liver disease

HCV infection has a significant effect on the health of persons with CKD. Hemodialysis patients infected with HCV have a higher mortality rate than non-infected hemodialysis patients, a result of an increased rate of progression to cirrhosis and/or hepatocellular carcinoma.²⁴⁹⁻²⁵¹ Moreover, patients with HCV infection who undergo kidney transplantation have reduced survival rates, as do their grafts.²⁵²⁻²⁵⁴ In addition, kidney transplant recipients who remain HCV-infected are at high risk of developing post-transplant diabetes mellitus²⁵⁵⁻²⁵⁷ as well as *de novo* membranous glomerulonephritis post-transplantation.²⁵⁸⁻²⁶⁰ Accordingly, there is general belief that persons with CKD who are infected with hepatitis C should be treated before they reach the need for kidney transplantation.²⁶¹

Despite the serious impact of HCV infection on persons with CKD, ALT levels are often lower in these patients than in persons with an equivalent grade of liver injury without kidney disease, and the values may even be normal.²⁶²⁻²⁶⁴ In one study, a wide discrepancy was noted between the level of the ALT and the extent of histologic damage.²⁶⁵ Accordingly, a liver biopsy is as important for these individuals as it is for persons who do not have CKD. There is some concern that, because platelet dysfunction is increased in persons with uremia, performing a liver biopsy in persons with CKD increases the risk of bleeding.²⁶⁶⁻²⁶⁸ Nevertheless, liver biopsies have been performed frequently in persons with CKD undergoing hemodialysis without leading to an increase in bleeding complications.^{265,269-271} A liver biopsy may therefore be performed in persons with renal insufficiency using the same guidelines as those used for persons without CKD.²⁷²

Testing for HCV infection should start with anti-HCV, followed by a highly sensitive assay for HCV RNA.²⁷³ Because of the high prevalence of HCV infection and its deleterious effects in these individuals, all persons with CKD should be tested for HCV infection regardless of the severity of the kidney disease or of the ALT level, in order to plan management and treatment.²⁶¹ If not already done, CKD patients should be tested for serum HCV RNA before the start of hemodialysis and both pre- and post-kidney transplantation. Screening for HCV infection should also be performed in hemodialysis patients with unexplained abnormalities of liver-related biochemical tests, and in all patients with possible nosocomial exposure to hepatitis C.²⁷³ Hemodialysis patients should be tested monthly for ALT and 6-monthly for anti-HCV followed by re-testing for HCV

Table 14. Treatment According to Stages of Chronic Kidney Diseases²⁷³

Stage	Description	GFR (ml min ⁻¹ 1.73 m ⁻²)	Recommended Treatment
1.	Kidney damage with normal or increased GFR	≥90	A
2.	Kidney damage with mild decrease GFR	60-90	A
3.	Moderate decrease GFR	30-59	B
4.	Severe decrease GFR	15-29	B
5.	Kidney failure	<15	B
5D.	Dialysis (hemo- or peritoneal)		C

A: Routine combination therapy according to viral genotype.

B: Peginterferon alfa-2b, 1 μg/kg subcutaneously once weekly, or Peginterferon alfa-2a, 135 μg subcutaneously once weekly plus Ribavirin, 200-800 mg/day in two divided doses starting with low dose and increasing gradually

C: Controversial: Standard interferon (2a or 2b) 3mU three times weekly, or Pegylated interferon alfa-2b, 1 μg/kg/week, or Pegylated interferon alfa-2a, 135 μg/kg/week ± Ribavirin in markedly reduced daily dose.

Abbreviation: GFR, glomerular filtration rate.

RNA if these parameters raise suspicion of a new infection.²⁷³

When HCV infection is identified in persons with CKD, interferon-based antiviral treatment must be considered, but the regimen will vary depending upon the expression of the kidney disease. For this purpose, CKD can be subdivided into four broad categories; (1) persons with early stage CKD identified by a decreased glomerular filtration rate (GFR) but not sufficient to warrant dialysis; (2) patients who require hemodialysis; (3) patients listed for and who undergo kidney transplantation, and (4) persons with HCV-related glomerulonephritis, most with associated cryoglobulinemia.

The decision to treat must take into account the competing severities of the CKD and the chronic liver disease, the risks of the treatment itself, whether or not hemodialysis is being contemplated, and whether there are comorbid conditions that may affect morbidity and mortality, such as cardiovascular disease. Of relevance is that the kidney plays a role in the catabolism and filtration of both interferon^{274,275} and ribavirin^{276,277} and thus their clearances may be affected in persons with kidney failure.^{278,279} The clearance of pegylated interferon is reduced in persons with kidney failure, although hemodialysis does not appear to affect clearance.^{280,281} Ribavirin is filtered by the kidneys, and therefore its clearance is impaired in persons with advanced kidney disease and it is not removed by dialysis. The result is an increased severity of hemolytic anemia among persons in whom anemia is already a problem.^{276,277} Consequently, as the kidney function begins to deteriorate, the concentration of both drugs must be reduced; indeed, ribavirin should be used with caution when the creatinine clearance falls to below 50 mL/minutes.²⁸² In limited research studies, reduced doses of ribavirin have been used, even when the creatinine clearance is low, together with both standard interferon,²⁸³ and pegylated interferon.²⁸² These regimens are associated with a very high rate of adverse events

and hence such treatment requires extremely close monitoring and often the added use of growth factors. Treatment regimens and their doses will therefore need to be considered in light of the severity of the CKD.

The therapeutic regimen varies with the severity of the kidney disease. Persons with slight to mild kidney disease (GFR >60 mL/minute), referred to as CKD stages 1 and 2 (Table 14), can be treated with the same regimen routinely administered to HCV-infected persons without kidney disease. For patients with worsening kidney function who are still pre-hemodialysis (CKD stages 3-5), treatment trials have been limited, with little available information to guide recommendations. Nevertheless, most experts support the cautious use of pegylated interferon alfa, adjusting the dose to the level of kidney dysfunction. The recommended doses for this group are peginterferon alfa-2b, 1 μg/kg subcutaneously once weekly or peginterferon alfa-2a, 135 μg subcutaneously once weekly, together with ribavirin, 200 to 800 mg per day in 2 divided doses, starting with the low dose and increasing gradually as long as side effects are minimal and manageable.²⁷³

There have been numerous, mostly small, studies of treatment of patients with HCV infection who are on hemodialysis (CKD stage 5D).²⁸³⁻²⁹⁹ These have included monotherapy with standard interferons²⁸⁵⁻²⁹⁰ leading to overall SVR rates of 33% to 37% with rates of 26% to 31% in persons with genotype 1 infection^{285,286} but associated with high dropout rates.^{285,288} Of note is that these SVR rates are higher than occurs in persons without kidney disease treated with standard interferon alone. Higher response rates have been reported in hemodialysis patients treated with standard interferon and reduced doses of ribavirin,^{283,289-291} with peginterferon alone,²⁹²⁻²⁹⁶ or peginterferon together with ribavirin,^{283,297} but these have been associated with very high frequencies of side effects, requiring growth factors to treat the anemia and neutropenia, high dropout rates, and high rates of relapse

on completion of treatment.^{283,289-291} Clearly, treatment of patients on hemodialysis is fraught with difficulty and requires meticulous attention to side effect management.

An international group of experts in both kidney and liver disease have recommended that if HCV-infected hemodialysis patients are considered for treatment, it should consist of standard interferon, alpha 2a or 2b, in preference to pegylated interferons, without the addition of ribavirin.²⁷³ The rationale for this recommendation is that standard interferon has appeared as effective as pegylated interferon in persons on hemodialysis because its excretion is reduced in these patients, its adverse effects are lower, and management of adverse effects is more difficult with pegylated than with standard interferons. The dose recommended is 3mU given subcutaneously three times a week.²⁷³ However, in a recently reported study, treatment of dialysis patients with peginterferon alfa-2a (135 µg per week) and low-dose ribavirin (200 mg/day) led to an SVR in 29% of HCV monoinfected patients (one-half with genotype 1) and in one-third of those coinfecting with HIV.³⁰⁰ The dropout rate was high (71.4%) due largely to the development of severe anemia, but the authors called for larger prospective, controlled clinical trials using combination therapy.³⁰⁰

There have also been small studies of treatment for patients with HCV infection who have undergone kidney transplantation because of their higher mortality rate than transplant patients not infected with HCV. Trials have included interferon alone,³⁰¹ interferon with low dose ribavirin,³⁰²⁻³⁰⁴ and ribavirin alone.³⁰⁴⁻³⁰⁶ Response rates have been low and graft rejection a consistent problem. Accordingly, routine interferon-based antiviral treatment post-kidney transplant is not recommended and should be considered only for persons who develop post-transplantation fibrosing cholestatic hepatitis.³⁰⁷

Treatment of cryoglobulinemia-associated glomerulonephritis also is challenging. Treatment with interferon may exacerbate the vasculitis,^{308,309} and therefore should be restricted to those with overt symptoms, with careful monitoring of renal function to ensure that the kidney disease is not worsened.²⁴⁵ Persons with progressive renal failure generally require treatment with immunosuppressive therapy with cyclophosphamide or rituximab, as well as plasmapheresis and pulsed steroids.^{310,311} The role of interferon-based antiviral therapy for hepatitis C in persons with cryoglobulinemia is still being defined but is considered useful for those with mild to moderate kidney disease or after the acute flare has been controlled with immunosuppressive agents.³¹² Trials with interferon alone,^{313,314} interferon with ribavirin,^{315,316} and pegylated interferon with ribavirin,³¹⁷⁻³¹⁹ have yielded mixed results. Because most of these studies have been small and

uncontrolled trials, there is no evidence-based data on which to base firm recommendations. Thus, it is suggested that persons with moderate proteinuria and slowly progressive kidney disease can be treated for 12 months either with standard interferon or with reduced doses of peginterferon, as described above.²⁷³ Treatment leads commonly to disappearance of the cryoglobulinemia and, in those treated with pegylated interferon plus ribavirin, to a high SVR (62.5%).

Recommendations

37. All persons with chronic kidney disease awaiting renal replacement therapy, namely hemodialysis or kidney transplantation, should be screened for hepatitis C in order to plan for management and treatment (Class I, Level B).

38. The decision to perform a liver biopsy in patients with kidney disease should be individualized, based upon the clinical assessment for the need for therapy and the need to establish the severity of the liver disease (Class IIa, Level C).

39. Persons with chronic HCV infection and mild kidney disease (GFR > 60 mL/minute) can be treated with the same combination antiviral therapy as that used in persons without kidney disease (Class IIa, Level C).

40. Persons with chronic HCV infection and severe kidney disease not undergoing hemodialysis can be treated with reduced doses of both peginterferon (alpha-2a, 135 µg/week; alpha-2b, 1 µg/kg/week) and ribavirin (200-800 mg/day) with careful monitoring for adverse effects (Class IIa, Level C).

41. 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, 135 µg/week or 2b 1 µg/kg/week. (Class IIa, level C). Ribavirin can be used in combination with interferon in a markedly reduced daily dose with careful monitoring for anemia and other adverse effects. (Class IIb, level C).

42. Treatment is not recommended for patients with chronic HCV infection who have undergone kidney transplantation, unless they develop fibrosing cholestatic hepatitis (Class III, Level C).

43. 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 (Class IIa, Level C).

44. 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 (Class IIa, Level C).

Treatment of African Americans. The prevalence in the U.S. of anti-HCV is higher in African Americans (3%) than in non-Hispanic whites, (1.5%) and Hispanics (1.3%).⁷ Compared to Caucasians, African Americans tend to have lower ALT levels for similar histologic activity, and milder liver histology but a higher rate of development of hepatocellular carcinoma.³²⁰ Especially concerning is that African Americans are less likely than non-Hispanic whites to respond to interferon-based therapies.

Two published studies using pegylated interferon and ribavirin were designed specifically to compare response rates between African Americans and non-Hispanic whites.^{321,322} In these two trials, SVR rates in African American with genotype 1 infections were 19% and 28% respectively, while both reported an SVR rate of 52% in non-Hispanic whites.^{321,322} The study reporting the lower SVR rate in African American subjects utilized a lower dose of ribavirin (1000 mg daily for 12 weeks, followed by 800 mg daily) than the second study, which used weight-based ribavirin dosing.³²¹ A third, community-based randomized trial was designed to compare a flat (800 mg/day) ribavirin dose to weight-based ribavirin in combination with pegylated interferon, and included sufficient African American subjects that permitted a subanalysis of treatment response in this population.³²³ In the treatment arm receiving weight-based ribavirin, SVR rates were 21% and 37% in African Americans and Caucasian patients, respectively.³²³ SVR rates were also reported to be lower among African American compared to Caucasian patients with HCV genotypes 2 and 3 infections.³²⁴

The reasons for this marked difference in response rates between African Americans and non-Hispanic Whites are unclear; in the NIH-sponsored study, the low response rate was independent of BMI, the presence of diabetes, viral subtype (1a versus 1b), viral levels, severity of liver disease, dose of peginterferon and ribavirin received or compliance.³²² Early virological kinetics and ETR were poorer in African Americans, suggesting perhaps a defect in antiviral response to either interferon or ribavirin.³²²

Baseline constitutional neutropenia is a more common finding in African Americans than Caucasians and may be a safety concern. In spite of this, African Americans do not appear to be at increased risk for serious infections or adverse events during peginterferon and ribavirin combination therapy.^{321,322,325} Since maintenance of full dose

Table 15. Modified Child-Turcotte-Pugh Score for Grading Severity of Liver Disease

Variable	1	2	3
Serum bilirubin, mg/dL	<2.0	2.0-3.0	>3.0
Serum albumin, g/dL	>3.5	2.8-3.5	<2.8
Prothrombin time INR	<1.7	1.7-2.3	>2.3
Ascites	None	Easily controlled	Poorly controlled
Encephalopathy	None	Minimal	Advanced coma

The score is calculated as the sum of the scores for albumin, bilirubin, prothrombin time, ascites and encephalopathy (range 5-15). Class A is defined as 5-6, class B as 7-9, and class C as 10-15.

peginterferon is important for achieving an SVR, some experts recommend not to reduce the initial or on-treatment dose of peginterferon in African-American patients unless the absolute neutrophil count is below 500 mm³.^{125,322}

Despite the diminished response in African Americans, their management should not differ from that of Caucasian patients. Because of the higher prevalence of HCV infection and lower response rates in African Americans, it is vital that this group of patients be adequately represented in future trials evaluating new agents for chronic HCV infection.

Recommendations

45. African Americans infected with HCV who are appropriate treatment candidates should be treated with the current optimal regimen consisting of pegylated interferon and ribavirin (Class I, Level A).

46. African Americans with baseline neutropenia (ANC \leq 1500 mm³) should not be excluded from hepatitis C treatment (Class IIa, Level B).

Treatment of Persons with Compensated and Decompensated Cirrhosis. Compensated cirrhosis is generally distinguished from decompensated cirrhosis by means of the CTP scoring system (Table 15). In the early registration treatment trials, patients who had HCV-related compensated cirrhosis did achieve SVRs but at lower rates than did those without cirrhosis.⁷¹⁻⁷³ Two subsequent treatment studies focused exclusively on persons with compensated cirrhosis.^{326,327} In the first, an SVR was reached in 30% of those treated with peginterferon alfa-2a alone although 10% developed neutropenia, reversible after treatment discontinuation.³²⁶ In the second that used peginterferon alfa-2a together with two different doses of ribavirin (1,000 to 1,200 mg per day or 600 to 800 mg. per day), an SVR was achieved in 52% of patients who received the standard ribavirin dose and in 38% of those treated with the low dose.³²⁷ Serious adverse events developed in 14% and 18% of recipients of the standard and low ribavirin doses, respectively, while dose

reduction was necessary in 78% and 57% of the two groups, respectively. Thus, patients with HCV-related compensated cirrhosis can be successfully treated but with an anticipated higher rate of developing adverse effects of treatment.

Treatment of patients with decompensated cirrhosis, defined as one or more of the clinical complications of chronic liver disease — ascites, encephalopathy, variceal bleeding, and/or impaired hepatic synthetic function — is more problematic. Their treatment of choice is liver transplantation, although variceal bleeding can be successfully managed without surgery, following which such patients can remain stable for a prolonged period before the need for transplantation arises. For those undergoing liver transplantation, reinfection of the allograft with HCV is the rule and progressive post-transplantation disease of the grafted liver is common.^{328,329} Accordingly, since eradication of HCV pre-transplantation is associated with a lower likelihood of post-transplantation infection, there is a strong incentive to treat the HCV infection before transplantation, provided the risks of treatment are acceptable. However, treatment commonly leads to serious adverse events, such as life-threatening infection and the possible acceleration of hepatic decompensation.

At least five groups have evaluated treatment for patients with decompensated cirrhosis preliminary to liver transplantation.³³⁰⁻³³⁴ In the earliest reported study, 32 patients awaiting liver transplantation were considered for antiviral treatment, but over one-half were found ineligible because of cytopenias.³³⁰ Among those treated with standard or low doses of interferon alfa-2b or low doses of both interferon alfa-2b and ribavirin, 33% became HCV RNA negative. Almost all developed adverse effects, most of which was graded as severe. In a second study, 30 patients with HCV-related cirrhosis destined for liver transplantation (half graded as CTP class A) were treated with interferon alfa-2b, 3 mU daily and ribavirin, 800 mg/day if their presumed time to liver transplantation was less than 4 months.³³¹ After a median treatment duration of 12 weeks, 30% responded to treatment and then underwent liver transplantation, 2/3 of whom remained HCV RNA negative over a median follow-up period of 46 weeks. Sixty percent developed neutropenia. Reported in the same year was a study of 20 patients, most with genotype 1 infection, who were treated before transplantation for a mean of 14 months with interferon alfa-2b in a dose of 5 mU daily.³³² At transplantation, 60% were HCV RNA negative, but only 20% remained negative after transplantation. A fourth study involved 124 patients with advanced cirrhosis (CTP classes A, B and C) treated mainly with interferon alfa-2b plus ribavirin, and less frequently, with pegylated interferon plus ribavirin.³³³

Treatment began with half doses that were increased incrementally as tolerated at 2 week intervals (referred to as a low accelerating dose regimen), and growth factors were used as needed. An SVR developed in 13% of patients with genotype 1 and in 50% with non-genotype 1 infections. Adverse events were frequent, requiring dose reductions or treatment termination, but among those who did become HCV RNA negative before transplantation, 80% remained negative 6 or more months after transplantation. The most recent study is the only one to include non-treated controls but these consisted of patients unwilling to participate in the study.³³⁴ The treatment administered was peginterferon alfa-2b, 1.0 $\mu\text{g}/\text{kg}$ body weight given weekly and ribavirin, 800 to 1000 mg daily for 24 weeks. An SVR developed in 44% of the patients with HCV genotypes 2 or 3, and in 7% of those with genotypes 1 or 4. Treatment had to be discontinued in 20%, was reduced in 39%, and was tolerated in 41%. Over a 30-month follow-up period, decompensated events occurred in 83% of the controls, 62% of the non-responders, and in 23% of the patients who had developed an SVR. The conclusion of this study was that antiviral therapy can be life-saving, improves hepatic function, and that treatment seems appropriate for persons with genotype 2 and 3 infections particularly in those with cirrhosis, CTP classes A and B.

Hematologic adverse events, including anemia, neutropenia and thrombocytopenia are more common in persons with than without cirrhosis, particularly those with clinically decompensated liver disease (See section on Adverse Events).

Recommendations

47. Patients with HCV-related compensated cirrhosis (CTP class A), can be treated with the standard regimen of pegylated interferon and ribavirin but will require close monitoring for adverse events (Class I, Level A).

48. Patients with HCV-related decompensated cirrhosis should be referred for consideration of liver transplantation (Class I, Level B).

49. Interferon-based therapy may be initiated at a lower dose in patients with decompensated cirrhosis (CTP class B and C), 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 (Class IIb, Level B).

50. Growth factors can be used for treatment-associated anemia and leukopenia to improve quality of life and may limit the need for antiviral dose reduc-

tions in patients with decompensated cirrhosis (Class IIb, Level C).

Treatment of Patients After Solid Organ Transplantation. The prevalence of hepatitis C infection in recipients of solid organ transplants varies depending on the organ received. Currently, 40% to 50% of liver recipients are infected with HCV, whereas the proportion of cardiac, lung, and kidney transplant recipients with HCV infection is lower. Recipients of heart, lung, or kidney transplants with post-transplantation HCV infection may have had HCV infection that predated transplantation or acquired their infection as a result of infected grafts, blood, or blood products, particularly before 1992, prior to the introduction of screening for HCV.¹⁵ Since then, the risk of acquiring HCV infection during the peri-transplant period has been very low. Hepatitis C viremia persists in most transplant recipients with pre-transplantation infection and progressive liver disease may affect survival post-solid organ transplantation.^{335,336} Immunosuppression administered to prevent allograft rejection likely plays a role in the accelerated liver disease observed in the post-transplantation setting.

Heart and Lung Transplantation. Reports are conflicting on the short-term outcome of graft and patient survival among recipients of hearts from anti-HCV positive donors compared to those who received hearts from anti-HCV negative donors. Early studies reported similar 5-year survival rates, 71% to 86% among heart transplant recipients who received anti-HCV positive donor hearts or acquired post-transplantation HCV infection compared with anti-HCV negative donors or those without post-transplant HCV infection.^{337,338} However, later studies report an increased rate of mortality from liver disease and the development of accelerated graft damage due to coronary vasculopathy in anti-HCV positive donors in heart transplant recipients compared with anti-HCV negative donors.^{339,340} Differences in reported outcome may be related to different immunosuppressive regimens, donor-recipient HLA mis-match, recipient age and severity of liver disease (in those transplanted with preexisting HCV infection).

Information on the outcome of lung transplantation in anti-HCV positive recipients comes from case reports only. In one report, 6 patients with chronic HCV infection (1 with cirrhosis on liver biopsy) underwent lung transplantation. Two deaths occurred, one at 8 months and the other at 2 years, none of which were liver-related.³⁴¹

Data on therapy of HCV infection in heart and lung recipients are derived from small case series.^{342,343} These reports indicate that interferon can be safely administered

and tolerated but response rates are poor. Until more data become available, administration of antiviral therapy should be made on an individual basis in anti-HCV positive heart and lung transplant recipients.

Liver Transplantation. Chronic HCV infection is the leading indication for liver transplantation in the adult U.S. population. Graft re-infection is almost universal and graft loss due to recurrent HCV occurs in approximately 25% to 30% of patients.^{344,345} Fibrosis progression may be accelerated in patients with recurrent HCV infection post-liver transplantation, with 6% to 23% of patients developing cirrhosis after a median of 3.4 years.^{328,346,347} Survival of patients with recurrent HCV infection post-liver transplantation is lower than in patients transplanted for other indications.³⁴⁸ Since HCV-related liver disease in this group is typically more progressive and survival reduced, as compared to the outcome among immune-competent individuals, many experts have advocated interferon-based antiviral therapy. However, the indications for treatment, the optimal timing, dose and duration of treatment for patients with recurrent HCV infection post-transplantation are not clear.

Therapy may be initiated preemptively, before the development of histological and biochemical recurrent hepatitis, or may be started once recurrent clinical disease is evident. Analyses of studies examining the efficacy of treatment for recurrent HCV infection are hampered by the enrollment of small numbers of patients at single centers, the use of different immunosuppressive regimens (which may play a role in the accelerated liver disease following liver transplantation), different criteria for initiating and stopping therapy, and finally, different treatment regimens among the various centers.

A preemptive strategy would seem attractive because treatment is begun while viral levels are low and before the graft is damaged and theoretically may lead to higher SVR rates. However, in practice, only 40% to 60% of patients are candidates because of the high doses of immunosuppression used, underlying cytopenias, mild renal dysfunction and the presence of other medical problems during this early period post-liver transplantation. The use of standard interferon or pegylated interferon monotherapy is not advised because of poor SVR rates, 0% and 8%, respectively as reported in randomized controlled trials.³⁴⁹⁻³⁵¹ Although the addition of ribavirin was associated with improved response rates, ribavirin is not well tolerated in the early peri-transplant period and dose reduction is common.^{352,353} Small, uncontrolled, trials of peginterferon plus ribavirin report SVR rates of 18% to 19%. In all studies, pre-emptive therapy was associated with high rates of side effects, including rejection and unrelated deaths, and a large proportion of patients re-

Table 16. Summary of Post-Liver Transplant Treatment Trials

Trial / Reference	N	Regimen	SVR (%)	Histological Response	D/C (%)	Dose Reduction (%)	Rejection
IFN vs RBV MonoRx RCT (1998 ³⁵⁵)	30	IFN- α 3MU tiw \times 24 weeks RBV up 10 1.2 g qd	0	No difference	0	21	
			0	Lobular inflammation improved	24	50	
IFN&RBV OL (2002 ³⁵⁶)	54	IFN 1.5-3MU tiw RBV 800-1000 mg qd \times 48 weeks	30		6	72	6
IFN &RBV vs no Rx RCT (2003 ³⁵⁷)	52	IFN- α 3 MU tiw RBV 800-1200 mg qd \times 48 weeks control	21	No difference in histology at end of follow-up	43		4
			0				
IFN&RBV OL (2003 ³⁵⁸)	54	IFN- α 3 MU tiw RBV 1000 mg qd \times 48	26		11		2
IFN/PegIFN&RBV OL (2006 ³⁵⁹)	31	IFN/RBV	13		40*	57*	3
	36	PegIFN/RBV	50				14
IFN&RBV OL (2004 ³⁶⁰)	24	IFN- α 3 MU tiw RBV 1000 mg qd \times 12 months RBV 600-1200 mg \times 6 months	13		29	88	
IFN&RBV OL (2005 ³⁶¹)	38	IFN- α 3 MU tiw RBV 800-1200 mg qd \times 48 weeks		No change in fibrosis	37	71	
PegIFN/RBV OL (2005 ³⁶²)	32	PegIFN 180 μ g q week RBV 1000-1200 mg qd \times 12 months	34		16	65	
PegIFN/RBV OL (2004 ³⁶³)	20	PegIFN 0.5-1 μ g q week RBV 400-800 mg qd	45	Improved	20	65	25
PegIFN/RBV OL (2005 ³⁶⁴)	24	PegIFN 1.5 μ g q week RBV 400-800 mg qd \times 48 weeks	35		13	58	
PegIFN/RBV OL (2006 ³⁶⁵)	25	PegIFN 1 μ g q week RBV 600 mg qd \times 48 weeks	36	Worsened fibrosis	4	52	0
PegIFN/RBV OL (2006 ³⁶⁶)	55	PegIFN 180/1.5 μ g/kg q week RBV 11 mg/kg/d \times 48 weeks	44	Inflammation improved. No change in fibrosis	7	29	2
PegIFN/RBV OL (2007 ³⁶⁷)	35	PegIFN 90-180 μ g/0.5-1.5 μ g/kg/week RBV 800 mg qd \times 48 weeks	37		43	74	11

*Total for both groups

quired dose reductions. Thus, given these adverse effects, the low SVR rates and the lack of improvement in graft loss or mortality, preemptive therapy cannot be universally recommended at present.

Most transplant centers prefer to delay therapy until recurrent disease is confirmed, either by persistently raised ALT levels unexplained by other causes, or by the demonstration of significant fibrosis on liver biopsy (Metavir and IASL stage ≥ 2 or Batts-Ludwig and Ishak stage ≥ 3).³⁵⁴ Therefore, unlike the non-transplant population, there is a lower threshold for performing liver biopsies in transplanted patients. The decision to initiate therapy must consider the benefits of achieving an SVR, including the potential for histologic improvement, versus the risk of precipitating acute cellular rejection and side effects of therapy. The early experience of interferon-based therapy post-liver transplantation was derived from small, uncontrolled, observational studies using either interferon monotherapy or its combination with ribavirin, results of which were generally disappointing (Table 16).

The combination of pegylated interferon alfa and ribavirin has not been shown to be superior to peginterferon monotherapy in the post-transplantation setting.³⁶⁸ The SVR rates were similar with monotherapy (38%) compared to combination therapy (33%). This is likely due to the poor tolerance of ribavirin in the post-transplant setting, the requirement for reduced initial doses and the frequent need for dose reduction. Studies suggest that patients with mild histological disease respond better compared to those with more advanced liver disease. In one study, HCV-infected patients with mild, recurrent hepatitis C (Metavir F0-F2) were randomized to receive peginterferon alfa-2b plus ribavirin for 48 weeks or to no treatment.³⁶⁹ Patients with severe recurrence (Metavir F3, F4 and cholestatic hepatitis) were treated. Forty-eight percent of patients with mild recurrent and 19% with severe recurrent HCV infection achieved an SVR compared to 0% of untreated controls. Accordingly, close monitoring of patients post-liver transplant by liver biopsy is

advised and if progressive fibrosis is noted, treatment should be instituted.

Predictors of response to treatment post-transplantation have not been well studied. A retrospective analysis of 35 patients with recurrent HCV infection post-liver transplantation who were treated with peginterferon alfa and ribavirin for a planned duration of 48 weeks identified lower baseline HCV RNA level, negativity for HCV RNA at week 12, and adherence to the treatment regimen as predictors of an SVR.

Adverse events were common in all trials of patients with recurrent HCV post-liver transplantation, cytopenias being the most common reported. The risk of acute cellular rejection is an important concern that has been difficult to estimate. Uncontrolled trials report rates of 11% to 30%,³⁷⁰⁻³⁷² but randomized trials report lower rates (0% to 5%).^{369,373,374} Profound graft dysfunction may occur after viral clearance, but this is not common and management needs to be elucidated. Efforts should be made to define criteria for diagnosis, therapy and to define the optimal timing, duration and dose to treat recurrent HCV post-liver transplant before the disease becomes severe. Once cirrhosis develops, hepatic decompensation is common,³⁷⁵ and results of re-transplantation are generally poor.^{376,377}

Recommendations

51. Treatment of HCV-related disease following liver transplantation should be initiated in appropriate candidates after demonstration of recurrent histologic disease but should be undertaken with caution and under the supervision of a physician experienced in transplantation (Class IIa, Level A).

52. Peginterferon alfa either with or without ribavirin should be the preferred regimen when treating patients with hepatitis C after liver transplantation (Class IIa, Level B).

53. Interferon-based therapy should not be used in recipients of heart, lung, and kidney grafts, except for patients who develop fibrosing cholestatic hepatitis (Class III, Level C).

Treatment of Persons with Acute Hepatitis C

The response rate to treatment is higher in persons with acute than with chronic HCV infection. However, the optimal treatment regimen and when it should be initiated remains uncertain.

There is consistent evidence that treatment reduces the risk that acute hepatitis C will evolve to chronic infection. Studies using high doses of interferon (5-10 million units per day) for at least 12 weeks, or until serum enzymes normalized, report sustained viral response rates of 83%

to 100%, which are much higher than any estimates of spontaneous clearance,^{378,379} or of response rates in persons with chronic HCV infection. One meta-analysis considered results of 16 trials that compared interferon therapy with spontaneous resolution of acute hepatitis C.³⁸⁰ There is remarkable consistency in the superiority of treatment in preventing evolution to chronic HCV infection when compared to observation. Overall, the pooled estimate of the treatment effect was a risk difference of 49% (95% CI 33-65), making it clear that treatment of acute hepatitis C reduces the risk of developing chronic infection.

The optimal regimen to treat acute HCV infection has not been definitively established. In one study from Germany, the most effective regimen at the time was administered to 60 patients diagnosed with acute hepatitis C.³⁸¹ The majority (85%) presented with symptomatic disease. None of those with asymptomatic acute hepatitis C spontaneously cleared virus, whereas 52% of those with symptomatic onset lost virus spontaneously, usually within 12 weeks. Treatment given to those who did not spontaneously lose virus, beginning 3 to 6 months after onset of disease, led to an SVR rate in 81%. Overall, 91% cleared virus either spontaneously or through treatment. The authors concluded that for those with symptomatic acute hepatitis, treatment should be delayed for the first 12 weeks. Further support for delaying treatment for up to 12 weeks came from another multi-center study of acute hepatitis C in which SVR rates >90% were reported for patients randomized to 12 weeks of peginterferon alfa-2b after delaying 8 or 12 weeks after diagnosis.³⁸² In contrast, a lower SVR rate (76%) was found for those randomized to delay peginterferon 20 weeks after diagnosis. In another study from Japan, 13 of 15 persons randomized to start within 8 weeks had an SVR compared to 8 of 15 in whom treatment was delayed by 12 months.³⁸³ Collectively, these data suggest that it is reasonable to start treatment within 8-12 weeks after identified acute hepatitis C, and thus patients should be monitored monthly for this purpose. Within this range, treatment might be delayed longer in persons presenting with jaundice and those with fluctuating viremia patterns that are associated with spontaneous clearance, while earlier treatment might be favored in persons with genotype 1 infection who have high (>800,000 log₁₀ IU/mL) viral loads.

There are few studies that address the regimen, dose, or duration. Several case series using variable doses of peginterferon alfa-2b for 12 weeks reported higher SVR rates in persons who received higher doses (>1.2-1.33 µg/kg/wk).^{384,385} However, aside from a trend toward a higher peginterferon dose, as of this time there are no definitive answers to whether concurrent use of ribavirin improves

SVR rates with acute HCV treatment, nor are there data establishing the benefit of peginterferon alfa or the comparability of 12 weeks to longer courses. Although HCV RNA in patients with acute infection generally is cleared from the blood by 8 to 16 weeks in most persons who recover spontaneously, viremia has been observed as late as 48 weeks after acute infection in injection drug users who ultimately clear.³⁸⁶⁻³⁸⁸ Thus, what is offered is an interim set of recommendations that will need modification as more data accumulate.

Recommendations

54. Patients with acute HCV infection should be considered for interferon-based anti-viral therapy (Class I, Level B).

55. Treatment can be delayed for 8 to 12 weeks after acute onset of hepatitis to allow for spontaneous resolution (Class IIa, Level B).

56. Although excellent results were achieved using standard interferon monotherapy, it is appropriate to consider the use of peginterferon because of its greater ease of administration (Class I, Level B).

57. Until more information becomes available, no definitive recommendation can be made about the optimal duration needed for treatment of acute hepatitis C; however, it is reasonable to treat for at least 12 weeks, and 24 weeks may be considered (Class IIa, Level B).

58. No recommendation can be made for or against the addition of ribavirin and the decision will therefore need to be considered on a case-by-case basis (Class IIa, Level C).

Treatment of Active Injection Drug Users

Illicit injection drug use is the predominant mode of HCV transmission, accounting for more than 60% of new cases in Western countries. Many individuals who acquired HCV infection from injection drug use discontinued the practice years before medical management of their infection began, and the standard guidelines outlined above apply. However, there is a wide spectrum of illicit drug use that includes persons of all socioeconomic strata and that varies in many respects: whether use is ongoing or took place in the distant past; whether illicit drug use is occasional or an uncontrollable daily need; whether heroin, cocaine, or other substances are used; and whether use is by injection or other modes. In addition, many who use illicit drugs transition between these stages. Thus, it is important to consider the individual issues that may affect the risks and benefits of treatment of HCV

infection in persons who use illicit drugs, rather than to make categorical recommendations.³⁸⁹

The use of methadone, naltrexone, or buprenorphine is an effective means of reducing illicit drug use and its complications.³⁹⁰ Although some *in vitro* studies have suggested that opiates diminish endogenous interferon alfa production,³⁹¹ there are several studies of persons taking methadone that suggest that the drug does not significantly reduce the likelihood of an SVR, nor does it alter the dosing of interferon alfa or ribavirin.^{392,393} Therefore, methadone use does not directly affect the management of HCV infection.

The benefits of treatment would be diminished substantially if a person were reinfected, which has been reported after spontaneous recovery both in humans and in experimental studies of chimpanzees.^{394,395} The risk of reinfection following an SVR in persons who use illicit drugs is not well established. In one study, 18 injection drug users who acquired SVR were followed and HCV RNA was detected again in two.³⁹⁶

For many individuals who are actively injecting illicit drugs, there is low willingness to undergo HCV treatment and diminished ability to adhere to treatment and precautions regarding contraception, and to maintain regular follow-up visits. For example, in one multicenter study, almost one half of young HCV-infected injection drug users had moderate or severe depression.³⁹⁷ Some illicit drug users, however — even those who use by injection — are willing and able to undergo treatment for HCV infection.^{393,398-400} For example, in one study, 76 persons taking methadone for heroin addiction were treated in a setting established to diminish treatment barriers.^{392,401} Of 76 treated, 21 achieved an SVR, an outcome that was less likely for those with pretreatment psychiatric disease but not active drug use.

Thus, there are a number of factors that determine the benefits and risks of HCV treatment in illicit drug users, and treatment decisions will need to be individualized accordingly. Many factors, such as the stage of liver disease and HCV genotype, are similar to persons who do not use illicit drugs. Special concerns include an increased risk of reinfection and, for select individuals, concerns about use of needles causing relapse into drug use. For persons who continue to inject illicit drugs, especially if they share needles and other drug-use equipment, efforts should generally be focused on providing addiction treatment. Ideally, HCV management is integrated with addiction treatment and delivered by multidisciplinary teams, including experienced drug abuse and psychiatric counseling services.

Recommendations

59. Treatment of HCV infection can be considered for persons even if they 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 (Class IIa, Level C)

60. Persons who use illicit drugs should receive continued support from drug abuse and psychiatric counseling services as an important adjunct to treatment of HCV infection (Class IIa, Level C).

Treatment of Persons with Psychiatric Illnesses

Patients with chronic HCV infection have a higher prevalence of psychiatric illness compared to the general U.S. population. The prevalence of chronic HCV infection in patients with mental or psychiatric diseases ranges from 8% to 31%, which is 4 to 20 times that of the U.S. population (1.8%). Mental or psychiatric disease represents a significant barrier to treatment in patients with chronic HCV infection. The argument against treatment of this population stems from the neuropsychiatric side effects associated with interferon and ribavirin therapy such as depression, irritability, suicidal ideation, mania, mood swings and relapse of drug or alcohol abuse.^{389,402} Persons with mental or psychiatric disorders are felt to be at higher risk for these side effects.⁴⁰² Significant depressive symptoms occur in 21% to 58% of interferon-treated patients. However, a recent prospective controlled trial demonstrated that these patients may be successfully treated with a multidisciplinary approach to management of adherence and neuropsychiatric side effects. Using this approach, they can achieve SVR rates that are similar to patients without psychiatric disorders.⁴⁰³

Most psychotropic agents are thought to be safe for use in the management of patients with chronic HCV infection and psychiatric disease. However, consideration should be given to drug–drug interactions and dose modification in patients with advanced liver disease. Despite the clinical challenges of HCV treatment in patients with mental and psychiatric disease, the available evidence is that interferon and ribavirin can be safely administered provided there is comprehensive pretreatment psychiatric assessment, a risk benefit analysis is conducted, and there are provisions for ongoing follow-up of neuropsychiatric symptoms during antiviral therapy by a multidisciplinary team.

Recommendations

61. Patients with HCV infection and concomitant mental and psychiatric disorders can be considered for

treatment using the currently approved regimens. (Class IIa, Level C).

62. Treatment of hepatitis C infection in patients with psychiatric disorders should be undertaken only with the support of a multi-disciplinary team that should include psychiatric counseling services (Class IIa, Level C).

General Management Issues

An important adjunct to the therapy of HCV is to advise chronically affected persons of measures that might be helpful in reducing or even preventing further fibrosis progression, independent of treatment. Most important is the issue of the potential deleterious effect of alcohol.

There are numerous studies that have reported a strong association between the use of excess alcohol and the development or progression of liver fibrosis and even the development of HCC.^{96,97,404–407} Moreover, excess alcohol intake may increase HCV RNA replication and interfere with response to treatment.^{408,409} Controversy exists, however, about the level of alcohol intake that is clearly harmful to the HCV-infected person. It is widely believed that the daily consumption of more than 50 grams of alcohol has a high likelihood of worsening the fibrosis, but there are reports of levels of alcohol intake of less than that amount having a deleterious effect on the liver disease.⁴¹⁰

Clearly, for heavy alcohol users, efforts should be undertaken to treat the alcohol abuse and dependence before starting treatment, but treatment is not contraindicated for persons who have an occasional drink of alcohol or who have a past history of alcoholism. Although no consensus opinion exists, it seems reasonable to recommend either the complete suspension of alcohol intake while on treatment or restricting its use to an occasional drink during the course of the treatment.

Obesity and its associated nonalcoholic fatty liver disease are believed to play a role in the progression of fibrosis in HCV-infected individuals and response to treatment.^{411,412} It is therefore appropriate to counsel those who are overweight (defined by a raised body mass index of >25 kg/m² or more) to attempt to lose weight. Additionally, weight reduction and improvement in insulin resistance may improve the response to peginterferon plus ribavirin therapy. This is sound advice for its potentially positive impact not only on the liver disease but also on the other conditions associated with being overweight.

A single report has suggested that superimposition of hepatitis A virus infection in persons with chronic liver disease, particularly those with hepatitis C, was associated with fulminant hepatitis.⁴¹³ Therefore, it is recommended that persons with chronic HCV infection who lack evidence of preexisting antibody to hepatitis A be

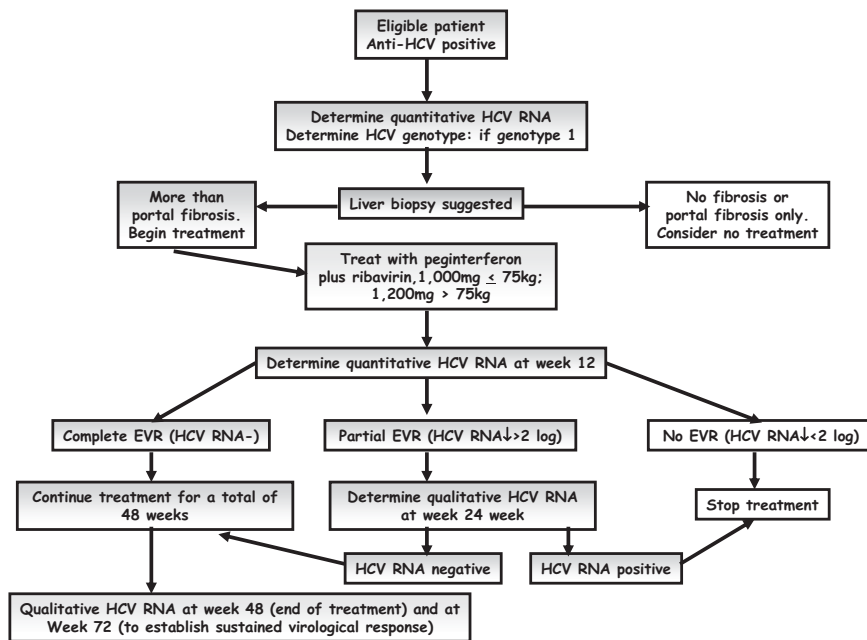


Fig. 3. Treatment algorithm for managing and treating patients with chronic HCV infection, genotype 1. SVR, sustained virologic response; EVR, early virologic response. RVR is omitted from this treatment algorithm because it has not yet been adequately evaluated. HCV RNA should be quantitated using a sensitive assay (10-50 IU/mL).

administered the hepatitis A vaccine.⁴¹⁴ Although no specific recommendation has been advanced for vaccination against hepatitis B, the evidence that persons co-infected with hepatitis B and C have a worse prognosis than those with HCV infection alone⁴¹⁵ suggests that hepatitis B vaccination should be offered to persons who are at risk for exposure to hepatitis B if they lack preexisting antibody to hepatitis B.

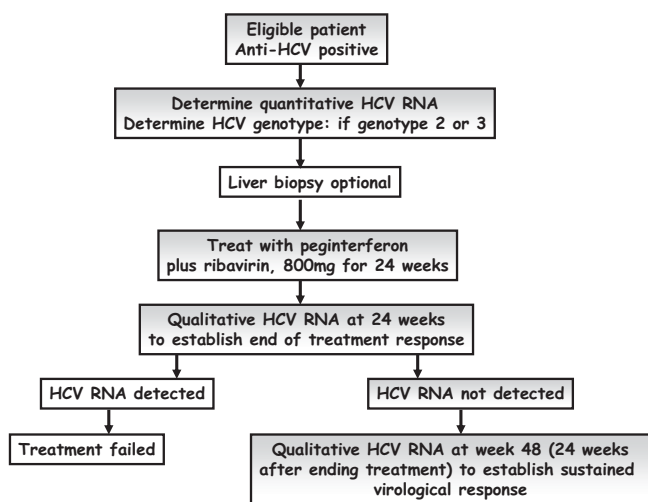


Fig. 4. Treatment algorithm for managing and treating patients with chronic HCV infection, genotype 2 or 3. EVR, early virologic response; ETR, end of treatment response; SVR, sustained virologic response. RVR is omitted from this treatment algorithm because it has not yet been adequately evaluated. HCV RNA should be quantitated using a sensitive assay (10-50 IU/mL).

Persons with chronic liver disease including those with hepatitis C frequently use herbal remedies.⁴¹⁶ In a prospective study, 42% of patients with chronic HCV infection reported using at least one herbal product.⁴¹⁷ Silymarin (milk thistle extract) was the most frequently reported herbal remedy used representing 72% of all herbals taken.⁴¹⁷ Similarly, approximately 40% of patients with advanced chronic hepatitis C and prior non-response to antiviral therapy who entered the long-term HALT-C treatment trial were found at the baseline visit to have either used herbal products in the past or were continuing to use them even while committing themselves to long-term peginterferon treatment.⁴¹⁸ Once again, silymarin was by far the preferred herbal. The benefit of silymarin or other herbal therapies for patients with chronic HCV infection has not been well studied or established. Currently, the NIH is conducting a well-designed scientific study of a standardized formulation of silymarin to determine its effectiveness in persons with chronic hepatitis C who had not responded to conventional medication, as well as among persons with non-alcoholic steatohepatitis (NASH). Of concern is that some herbals, particularly herbal mixtures have been associated with severe hepatotoxicity, fulminant hepatitis and death.⁴¹⁹ Accordingly, patients with chronic HCV infection should seek advice from their physician prior to initiating any herbal preparation. Similarly, prescription medications should be limited to the absolute minimum, particularly in those with cirrhosis.

Persons with chronic HCV infection should not share items of personal hygiene such as razors and toothbrushes.

Recommendations

63. All persons with chronic HCV infection who lack antibodies to hepatitis A and B should be offered vaccination against these two viral infections (Class IIa, Level C).

64. Persons with chronic HCV infection should be advised to abstain from alcohol consumption (Class IIb, Level C).

65. No recommendation can be made for the use of herbal products. There is no current evidence that herbal products have a role in the treatment of patients with acute or chronic HCV infection, (Class III, level C).

Conclusions

Described above are the current data on testing, diagnosis, decisions regarding whom to treat, and the recommended treatments of patients with chronic HCV infection. Figures 3 and 4 summarize the sequential steps recommended for managing and treating persons chronically infected with hepatitis C for whom treatment is considered clearly appropriate. As noted earlier, these represent currently acceptable guidelines; it is recognized that reasonable physicians may deviate from the strategy and remain within acceptable standards of treatment.

The issue of treatment of chronic HCV infection is in constant flux. There is highly active clinical research in this area, and new information appears with increasing frequency. Presented here is the current state of the art for management and treatment of persons with chronic HCV infection. However, these recommendations will need to be revised and updated in the future as additional critical and pivotal information becomes available.

Acknowledgment: This update of a previously published practice guideline was produced in collaboration with the Practice Guidelines Committee of the American Association for the Study of Liver Diseases. This committee supplied extensive peer-review of the manuscript. Members of the AASLD Practice Guidelines Committee include Margaret C. Shuhart, M.D., M.S., (Committee Chair), Gary L. Davis, M.D. (Board Liaison), Kiran Bambha, M.D., Andres Cardenas, MD, MMSc., Timothy J. Davern, M.D., José Franco, M.D., Steven-Huy B. Han, M.D., Stephen A. Harrison, M.D., Charles D. Howell, M.D., Simon C. Ling, MBChB, MRCP, Lawrence U. Liu, M.D., Paul Martin, M.D., Robert S. O'Shea, M.D., Nancy Reau, M.D., Bruce A. Runyon, M.D., Jayant A.

Talwalkar, M.D., MPH, John B. Wong, M.D., and Colina Yim, RN. M.N. The authors and the committee would like to acknowledge the contributions of Teresa L. Wright, MD to the previous version of this guideline.

References

- Eddy D. A manual for assessing health practices and designing practice guidelines. Philadelphia. American College of Physicians 1996:1-126.
- American Gastroenterological Association policy statement on the use of medical practice guidelines by managed care organizations and insurance carriers. *Gastroenterology* 1995;108:925-926.
- <http://www.heart.org/presenter.jhtml?identifier=3039683MMFAApAaa>.
- Shiffman RN, Shekelle P, Overhage JM, Slutsky J, Grimshaw J, Deshpande AM. Standardized reporting of clinical practice guidelines: a proposal from the Conference on Guideline Standardization. *Ann Intern Med* 2003;139:493-498.
- Williams R. Global challenges in liver disease. *HEPATOLOGY* 2006;44:521-526.
- www.who.int/immunization/topics/hepatitis_c/en/.
- Armstrong GL, Wasley A, Simard EP, McQuillan GM, Kuhnert WL, Alter MJ. The prevalence of hepatitis C virus infection in the United States, 1999 through 2002. *Ann Intern Med* 2006;144:705-714.
- Kim WR. The burden of hepatitis C in the United States. *HEPATOLOGY* 2002;36(Suppl):S30-S34.
- Deuffic-Burban S, Poynard T, Sulkowski MS, Wong JB. Estimating the future health burden of chronic hepatitis C and human immunodeficiency virus infections in the United States. *J Viral Hepat* 2007;14:107-115.
- Alter MJ, Seeff LB, Bacon BR, Thomas DL, Rigsby MO, Di Bisceglie AM. Testing for hepatitis C virus infection should be routine for persons at increased risk for infection. *Ann Intern Med* 2004;141:715-717.
- Alter MJ. Prevention of spread of hepatitis C. *HEPATOLOGY* 2002;36(Suppl):S93-S98.
- Wasley A, Miller JT, Finelli L. Surveillance for acute viral hepatitis — United States, 2005. *MMWR Surveill Summ* 2007;56:1-24.
- Schreiber GB, Busch MP, Kleinman SH, Korelitz JJ. The risk of transfusion-transmitted viral infections. *The Retrovirus Epidemiology Donor Study*. *N Engl J Med* 1996;334:1685-1690.
- Goedert JJ, Chen BE, Preiss L, Aledort LM, Rosenberg PS. Reconstruction of the hepatitis C virus epidemic in the US hemophilia population, 1940-1990. *Am J Epidemiol* 2007;165:1443-1453.
- Centers for Disease Control and Prevention. Recommendations for prevention and control of hepatitis C virus (HCV) infection and HCV-related chronic disease. *MMWR Recomm Rep* 1998;47:1-39.
- Jonas MM. Children with hepatitis C. *HEPATOLOGY* 2002;36(Suppl):S173-S178.
- Mast EE, Hwang LY, Seto DS, Nolte FS, Nainan OV, Wurtzel H, et al. Risk factors for perinatal transmission of hepatitis C virus (HCV) and the natural history of HCV infection acquired in infancy. *J Infect Dis* 2005;192:1880-1889.
- Workowski KA, Berman SM. Sexually transmitted diseases treatment guidelines, 2006. *MMWR Recomm Rep* 2006;55:1-94.
- Terrault NA. Sexual activity as a risk factor for hepatitis C. *HEPATOLOGY* 2002;36(Suppl):S99-S105.
- Puro V, Petrosillo N, Ippolito G. Risk of hepatitis C seroconversion after occupational exposures in health care workers. Italian Study Group on Occupational Risk of HIV and Other Bloodborne Infections. *Am J Infect Control* 1995;23:273-277.
- Forns X, Martinez-Bauer E, Feliu A, Garcia-Retortillo M, Martin M, Gay E, Navasa M, Sanchez-Tapias JM, Bruguera M, Rodes J. Nosocomial transmission of HCV in the liver unit of a tertiary care center. *HEPATOLOGY* 2005;41:115-122.
- Conte D, Fraquelli M, Prati D, Colucci A, Minola E. Prevalence and clinical course of chronic hepatitis C virus (HCV) infection and rate of

- HCV vertical transmission in a cohort of 15,250 pregnant women. *HEPATOLOGY* 2000;31:751-755.
23. Conry-Cantilena C, VanRaden M, Gibble J, Melpolder J, Shakil AO, Viladomiu L, et al. Routes of infection, viremia, and liver disease in blood donors found to have hepatitis C virus infection. *N Engl J Med* 1996; 334:1691-1696.
 24. Mele A, Corona R, Tosti ME, Palumbo F, Moiraghi A, Novaco F, et al. Beauty treatments and risk of parenterally transmitted hepatitis: results from the hepatitis surveillance system in Italy. *Scand J Infect Dis* 1995; 27:441-444.
 25. Sun DX, Zhang FG, Geng YQ, Xi DS. Hepatitis C transmission by cosmetic tattooing in women. *Lancet* 1996;347:541.
 26. Hwang LY, Kramer JR, Troisi C, Bull L, Grimes CZ, Lyerla R, et al. Relationship of cosmetic procedures and drug use to hepatitis C and hepatitis B virus infections in a low-risk population. *HEPATOLOGY* 2006; 44:341-351.
 27. Tumminelli F, Marcellin P, Rizzo S, Barbera S, Corvino G, Furia P, et al. Shaving as potential source of hepatitis C virus infection. *Lancet* 1995; 345:658.
 28. Mansell CJ, Locarnini SA. Epidemiology of hepatitis C in the East. *Semin Liver Dis* 1995;15:15-32.
 29. Briggs ME, Baker C, Hall R, Gaziano JM, Gagnon D, Bzowej N, et al. Prevalence and risk factors for hepatitis C virus infection at an urban Veterans Administration medical center. *HEPATOLOGY* 2001;34:1200-1205.
 30. Balasekaran R, Bulterys M, Jamal MM, Quinn PG, Johnston DE, Skipper B, et al. A case-control study of risk factors for sporadic hepatitis C virus infection in the southwestern United States. *Am J Gastroenterol* 1999;94:1341-1346.
 31. Laumann AE, Derick AJ. Tattoos and body piercings in the United States: a national data set. *J Am Acad Dermatol* 2006;55:413-421.
 32. Carroll ST, Riffenburgh RH, Roberts TA, Myhre EB. Tattoos and body piercings as indicators of adolescent risk-taking behaviors. *Pediatrics* 2002;109:1021-1027.
 33. Antoszewski B, Sitek A, Jedrzejczak M, Kasielska A, Kruk-Jeromin J. Are body piercing and tattooing safe fashions? *Eur J Dermatol* 2006;16:572-575.
 34. Colin C, Lanoir D, Touzet S, Meyaud-Kraemer L, Bailly F, Trepo C. Sensitivity and specificity of third-generation hepatitis C virus antibody detection assays: an analysis of the literature. *J Viral Hepat* 2001;8:87-95.
 35. Thio CL, Nolt KR, Astemborski J, Vlahov D, Nelson KE, Thomas DL. Screening for hepatitis C virus in human immunodeficiency virus-infected individuals. *J Clin Microbiol* 2000;38:575-577.
 36. Kalantar-Zadeh K, Miller LG, Daar ES. Diagnostic discordance for hepatitis C virus infection in hemodialysis patients. *Am J Kidney Dis* 2005; 46:290-300.
 37. Chamot E, Hirschel B, Wintsh J, Robert CF, Gabriel V, Deglon JJ, et al. Loss of antibodies against hepatitis C virus in HIV-seropositive intravenous drug users. *Aids* 1990;4:1275-1277.
 38. Dufour DR, Talastas M, Fernandez MD, Harris B, Strader DB, Seeff LB. Low-positive anti-hepatitis C virus enzyme immunoassay results: an important predictor of low likelihood of hepatitis C infection. *Clin Chem* 2003;49:479-486.
 39. Alter MJ, Kuhnert WL, Finelli L. Guidelines for laboratory testing and result reporting of antibody to hepatitis C virus. Centers for Disease Control and Prevention. *MMWR Recomm Rep* 2003;52:1-13, 15; quiz CE1-4.
 40. Pawlotsky JM, Lonjon I, Hezode C, Raynard B, Darthuy F, Remire J, et al. What strategy should be used for diagnosis of hepatitis C virus infection in clinical laboratories? *HEPATOLOGY* 1998;27:1700-1702.
 41. Stramer SL, Caglioti S, Strong DM. NAT of the United States and Canadian blood supply. *Transfusion* 2000;40:1165-1168.
 42. Pawlotsky JM. Molecular diagnosis of viral hepatitis. *Gastroenterology* 2002;122:1554-1568.
 43. Scott JD, Gretch DR. Molecular diagnostics of hepatitis C virus infection: a systematic review. *Jama* 2007;297:724-732.
 44. Saldanha J, Lelie N, Heath A. Establishment of the first international standard for nucleic acid amplification technology (NAT) assays for HCV RNA. WHO Collaborative Study Group. *Vox Sang* 1999;76:149-158.
 45. Pawlotsky JM, Bouvier-Alias M, Hezode C, Darthuy F, Remire J, Dhumeaux D. Standardization of hepatitis C virus RNA quantification. *HEPATOLOGY* 2000;32:654-659.
 46. Simmonds P, Bukh J, Combet C, Deleage G, Enomoto N, Feinstone S, et al. Consensus proposals for a unified system of nomenclature of hepatitis C virus genotypes. *HEPATOLOGY* 2005;42:962-973.
 47. Nainan OV, Alter MJ, Kruszon-Moran D, Gao FX, Xia G, McQuillan G, et al. Hepatitis C virus genotypes and viral concentrations in participants of a general population survey in the United States. *Gastroenterology* 2006;131:478-484.
 48. Germer JJ, Rys PN, Thorvilson JN, Persing DH. Determination of hepatitis C virus genotype by direct sequence analysis of products generated with the Amplicor HCV test. *J Clin Microbiol* 1999;37:2625-2630.
 49. Kleiner DE. The liver biopsy in chronic hepatitis C: a view from the other side of the microscope. *Semin Liver Dis* 2005;25:52-64.
 50. Scheuer PJ. Classification of chronic viral hepatitis: a need for reassessment. *J Hepatol* 1991;13:372-374.
 51. Desmet VJ, Gerber M, Hoofnagle JH, Manns M, Scheuer PJ. Classification of chronic hepatitis: diagnosis, grading and staging. *HEPATOLOGY* 1994;19:1513-1520.
 52. Batts KP, Ludwig J. Chronic hepatitis. An update on terminology and reporting. *Am J Surg Pathol* 1995;19:1409-1417.
 53. Bedossa P, Poynard T. An algorithm for the grading of activity in chronic hepatitis C. The METAVIR Cooperative Study Group. *HEPATOLOGY* 1996;24:289-293.
 54. Ishak K, Baptista A, Bianchi L, Callea F, De Groote J, Gudat F, et al. Histological grading and staging of chronic hepatitis. *J Hepatol* 1995;22: 696-699.
 55. Rubbia-Brandt L, Fabris P, Paganin S, Leandro G, Male PJ, Giostra E, et al. Steatosis affects chronic hepatitis C progression in a genotype specific way. *Gut* 2004;53:406-412.
 56. Poynard T, Ratzu V, McHutchison J, Manns M, Goodman Z, Zeuzem S, et al. Effect of treatment with peginterferon or interferon alfa-2b and ribavirin on steatosis in patients infected with hepatitis C. *HEPATOLOGY* 2003;38:75-85.
 57. Olynyk JK, Reddy KR, Di Bisceglie AM, Jeffers LJ, Parker TI, Radick JL, et al. Hepatic iron concentration as a predictor of response to interferon alfa therapy in chronic hepatitis C. *Gastroenterology* 1995;108:1104-1109.
 58. Westin J, Lagging M, Dhillon AP, Norkrans G, Romero AI, Pawlotsky JM, et al. Impact of hepatic steatosis on viral kinetics and treatment outcome during antiviral treatment of chronic HCV infection. *J Viral Hepat* 2007;14:29-35.
 59. Patton HM, Patel K, Behling C, Bylund D, Blatt LM, Vallee M, et al. The impact of steatosis on disease progression and early and sustained treatment response in chronic hepatitis C patients. *J Hepatol* 2004;40: 484-490.
 60. Fontana RJ, Israel J, LeClair P, Banner BF, Tortorelli K, Grace N, et al. Iron reduction before and during interferon therapy of chronic hepatitis C: results of a multicenter, randomized, controlled trial. *HEPATOLOGY* 2000;31:730-736.
 61. Reiss G, Keeffe EB. Role of liver biopsy in the management of chronic liver disease: selective rather than routine. *Rev Gastroenterol Disord* 2005;5:195-205.
 62. Crockett SD, Kaltenbach T, Keeffe EB. Do we still need a liver biopsy? Are the serum fibrosis tests ready for prime time? *Clin Liver Dis* 2006; 10:513-534, viii.
 63. Dienstag JL. The role of liver biopsy in chronic hepatitis C. *HEPATOLOGY* 2002;36(Suppl):S152-S160.
 64. Cadranet JF, Rufat P, Degos F. Practices of liver biopsy in France: results of a prospective nationwide survey. For the Group of Epidemiology of the French Association for the Study of the Liver (AFEF). *HEPATOLOGY* 2000;32:477-481.

65. Regev A, Berho M, Jeffers LJ, Milikowski C, Molina EG, Pappas M, et al. Sampling error and intraobserver variation in liver biopsy in patients with chronic HCV infection. *Am J Gastroenterol* 2002;97:2614-2618.
66. Rockey DC, Bissell DM. Noninvasive measures of liver fibrosis. *HEPATOLOGY* 2006;43(Suppl):S113-S120.
67. Sandrin L, Fourquet B, Hasquenoph JM, Yon S, Fournier C, Mal F, et al. Transient elastography: a new noninvasive method for assessment of hepatic fibrosis. *Ultrasound Med Biol* 2003;29:1705-1713.
68. Castera L, Vergniol J, Foucher J, Le Bail B, Chanteloup E, Haaser M, et al. Prospective comparison of transient elastography, Fibrotest, APRI, and liver biopsy for the assessment of fibrosis in chronic hepatitis C. *Gastroenterology* 2005;128:343-350.
69. Arena U, Vizzutti F, Corti G, Ambu S, Stasi C, Bresci S, et al. Acute viral hepatitis increases liver stiffness values measured by transient elastography. *HEPATOLOGY* 2008;47:380-384.
70. Sagir A, Erhardt A, Schmitt M, Haussinger D. Transient elastography is unreliable for detection of cirrhosis in patients with acute liver damage. *HEPATOLOGY* 2008;47:592-595.
71. Manns MP, McHutchison JG, Gordon SC, Rustgi VK, Shiffman M, Reindollar R, et al. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. *Lancet* 2001;358:958-965.
72. Fried MW, Shiffman ML, Reddy KR, Smith C, Marinos G, Goncalves FL, Jr., et al. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. *N Engl J Med* 2002;347:975-982.
73. Hadziyannis SJ, Sette H Jr, Morgan TR, Balan V, Diago M, Marcellin P, et al. Peginterferon-alpha2a and ribavirin combination therapy in chronic hepatitis C: a randomized study of treatment duration and ribavirin dose. *Ann Intern Med* 2004;140:346-355.
74. Alter HJ, Seeff LB. Recovery, persistence, and sequelae in hepatitis C virus infection: a perspective on long-term outcome. *Semin Liver Dis* 2000;20:17-35.
75. Levine RA, Sanderson SO, Ploutz-Snyder R, Murray F, Kay E, Hegarty J, et al. Assessment of fibrosis progression in untreated Irish women with chronic hepatitis C contracted from immunoglobulin anti-D. *Clin Gastroenterol Hepatol* 2006;4:1271-1277.
76. Thomas DL, Seeff LB. Natural history of hepatitis C. *Clin Liver Dis* 2005;9:383-398, vi.
77. Wong JB, Koff RS. Watchful waiting with periodic liver biopsy versus immediate empirical therapy for histologically mild chronic hepatitis C. A cost-effectiveness analysis. *Ann Intern Med* 2000;133:665-675.
78. Martinot-Peignoux M, Boyer N, Cazals-Hatem D, Pham BN, Gervais A, Le Breton V, et al. Prospective study on anti-hepatitis C virus-positive patients with persistently normal serum alanine transaminase with or without detectable serum hepatitis C virus RNA. *HEPATOLOGY* 2001;34:1000-1005.
79. Shiffman ML, Diago M, Tran A, Pockros P, Reindollar R, Prati D, et al. Chronic hepatitis C in patients with persistently normal alanine transaminase levels. *Clin Gastroenterol Hepatol* 2006;4:645-652.
80. Boccato S, Pistis R, Noventa F, Guido M, Benvegna L, Alberti A. Fibrosis progression in initially mild chronic hepatitis C. *J Viral Hepat* 2006;13:297-302.
81. Persico M, Persico E, Suozzo R, Conte S, De Seta M, Coppola L, et al. Natural history of hepatitis C virus carriers with persistently normal aminotransferase levels. *Gastroenterology* 2000;118:760-764.
82. Yu ML, Dai CY, Lee LP, Hou NJ, Hsieh MY, Huang JF, et al. A 24-week course of high-dose interferon-alpha plus ribavirin for Taiwanese chronic hepatitis C patients with persistently normal or near-normal alanine aminotransferase levels. *Liver Int* 2006;26:1187-1195.
83. Jacobson IM, Ahmed F, Russo MW, Lebovics E, Dieterich DT, Esposito SP, et al. Interferon alfa-2b [correction of alpha-2b] and ribavirin for patients with chronic hepatitis C and normal ALT. *Am J Gastroenterol* 2004;99:1700-1705.
84. Zeuzem S, Diago M, Gane E, Reddy KR, Pockros P, Prati D, et al. Peginterferon alfa-2a (40 kilodaltons) and ribavirin in patients with chronic hepatitis C and normal aminotransferase levels. *Gastroenterology* 2004;127:1724-1732.
85. Strader DB, Seeff LB. The natural history of chronic hepatitis C infection. *Eur J Gastroenterol Hepatol* 1996;8:324-328.
86. Seeff LB, Hoofnagle JH. National Institutes of Health Consensus Development Conference: management of hepatitis C: 2002. *HEPATOLOGY* 2002;36(Suppl):S1-S2.
87. Seeff LB. Natural history of chronic hepatitis C. *HEPATOLOGY* 2002;36(Suppl):S35-S46.
88. Liang TJ, Rehermann B, Seeff LB, Hoofnagle JH. Pathogenesis, natural history, treatment, and prevention of hepatitis C. *Ann Intern Med* 2000;132:296-305.
89. Kenny-Walsh E. Clinical outcomes after hepatitis C infection from contaminated anti-D immune globulin. Irish HEPATOLOGY Research Group. *N Engl J Med* 1999;340:1228-1233.
90. Wiese M, Berr F, Lafrenz M, Porst H, Oesen U. Low frequency of cirrhosis in a hepatitis C (genotype 1b) single-source outbreak in Germany: a 20-year multicenter study. *HEPATOLOGY* 2000;32:91-96.
91. Wiese M, Grungreiff K, Guthoff W, Lafrenz M, Oesen U, Porst H. Outcome in a hepatitis C (genotype 1b) single source outbreak in Germany—a 25-year multicenter study. *J Hepatol* 2005;43:590-598.
92. Vogt M, Lang T, Frosner G, Klingler C, Sendl AF, Zeller A, et al. Prevalence and clinical outcome of hepatitis C infection in children who underwent cardiac surgery before the implementation of blood-donor screening. *N Engl J Med* 1999;341:866-870.
93. Tong MJ, el-Farra NS, Reikes AR, Co RL. Clinical outcomes after transfusion-associated hepatitis C. *N Engl J Med* 1995;332:1463-1466.
94. Yano M, Kumada H, Kage M, Ikeda K, Shimamatsu K, Inoue O, et al. The long-term pathological evolution of chronic hepatitis C. *HEPATOLOGY* 1996;23:1334-1340.
95. Benhamou Y, Bochet M, Di Martino V, Charlotte F, Azria F, Coutellier A, et al. Liver fibrosis progression in human immunodeficiency virus and hepatitis C virus coinfecting patients. The Multivirc Group. *HEPATOLOGY* 1999;30:1054-1058.
96. Poynard T, Bedossa P, Opolon P. Natural history of liver fibrosis progression in patients with chronic hepatitis C. The OBSVIRC, METAVIR, CLINIVIR, and DOSVIRC groups. *Lancet* 1997;349:825-832.
97. Harris DR, Gonin R, Alter HJ, Wright EC, Buskell ZJ, Hollinger FB, et al. The relationship of acute transfusion-associated hepatitis to the development of cirrhosis in the presence of alcohol abuse. *Ann Intern Med* 2001;134:120-124.
98. Powell EE, Jonsson JR, Clouston AD. Steatosis: co-factor in other liver diseases. *HEPATOLOGY* 2005;42:5-13.
99. Fattovich G, Giustina G, Degos F, Tremolada F, Diodati G, Almasio P, et al. Morbidity and mortality in compensated cirrhosis type C: a retrospective follow-up study of 384 patients. *Gastroenterology* 1997;112:463-472.
100. Fontaine H, Nalpas B, Poulet B, Carnot F, Zylberberg H, Brechot C, et al. Hepatitis activity index is a key factor in determining the natural history of chronic hepatitis C. *Hum Pathol* 2001;32:904-909.
101. National Institutes of Health Consensus Development Conference Statement: Management of hepatitis C: 2002—June 10-12, 2002. *HEPATOLOGY* 2002;36:S3-S20.
102. Kobayashi S, Takeda T, Enomoto M, Tamori A, Kawada N, Habu D, et al. Development of hepatocellular carcinoma in patients with chronic hepatitis C who had a sustained virological response to interferon therapy: a multicenter, retrospective cohort study of 1124 patients. *Liver Int* 2007;27:186-191.
103. Yu JW, Wang GQ, Sun LJ, Li XG, Li SC. Predictive value of rapid virological response and early virological response on sustained virological response in HCV patients treated with pegylated interferon alpha-2a and ribavirin. *J Gastroenterol Hepatol* 2007;22:832-836.
104. Jensen DM, Morgan TR, Marcellin P, Pockros PJ, Reddy KR, Hadziyannis SJ, et al. Early identification of HCV genotype 1 patients responding to 24 weeks peginterferon alpha-2a (40 kd)/ribavirin therapy. *HEPATOLOGY* 2006;43:954-960.

105. Davis GL, Wong JB, McHutchison JG, Manns MP, Harvey J, Albrecht J. Early virologic response to treatment with peginterferon alfa-2b plus ribavirin in patients with chronic hepatitis C. *HEPATOLOGY* 2003;38:645-652.
106. Carlsson T, Reichard O, Norkrans G, Blackberg J, Sangfelt P, Wallmark E, et al. Hepatitis C virus RNA kinetics during the initial 12 weeks treatment with pegylated interferon-alpha 2a and ribavirin according to virological response. *J Viral Hepat* 2005;12:473-480.
107. Ferenci P, Fried MW, Shiffman ML, Smith CI, Marinus G, Goncalves FL Jr, et al. Predicting sustained virological responses in chronic hepatitis C patients treated with peginterferon alfa-2a (40 KD)/ribavirin. *J Hepatol* 2005;43:425-433.
108. Zeuzem S, Welsch C, Herrmann E. Pharmacokinetics of peginterferons. *Semin Liver Dis* 2003;23(Suppl 1):23-28.
109. Jacobson IM, Brown RS Jr, Freilich B, Afdhal N, Kwo PY, Santoro J, et al. Peginterferon alfa-2b and weight-based or flat-dose ribavirin in chronic hepatitis C patients: a randomized trial. *HEPATOLOGY* 2007;46:971-981.
110. Khuroo MS, Khuroo MS, Dahab ST. Meta-analysis: a randomized trial of peginterferon plus ribavirin for the initial treatment of chronic hepatitis C genotype 4. *Aliment Pharmacol Ther* 2004;20:931-938.
111. Kamal SM, El Kamary SS, Shardell MD, Hashem M, Ahmed IN, Muhammadi M, et al. Pegylated interferon alpha-2b plus ribavirin in patients with genotype 4 chronic hepatitis C: The role of rapid and early virologic response. *HEPATOLOGY* 2007;46:1732-1740.
112. Nguyen MH, Trinh HN, Garcia R, Nguyen G, Lam KD, Keeffe EB. Higher rate of sustained virologic response in chronic hepatitis C genotype 6 treated with 48 weeks versus 24 weeks of peginterferon plus ribavirin. *Am J Gastroenterol* 2008;103:1131-1135.
113. Romero-Gomez M, Del Mar Vitoria M, Andrade RJ, Salmeron J, Diago M, Fernandez-Rodriguez CM, et al. Insulin resistance impairs sustained response rate to peginterferon plus ribavirin in chronic hepatitis C patients. *Gastroenterology* 2005;128:636-641.
114. Shiffman ML, Suter F, Bacon BR, Nelson D, Harley H, Sola R, et al. Peginterferon alfa-2a and ribavirin for 16 or 24 weeks in HCV genotype 2 or 3. *N Engl J Med* 2007;357:124-134.
115. Zeuzem S, Buti M, Ferenci P, Sperl J, Horsmans Y, Cianciara J, et al. Efficacy of 24 weeks treatment with peginterferon alfa-2b plus ribavirin in patients with chronic hepatitis C infected with genotype 1 and low pre-treatment viremia. *J Hepatol* 2006;44:97-103.
116. Dalgard O, Bjoro K, Hellum KB, Myrvang B, Ritland S, Skaug K, et al. Treatment with pegylated interferon and ribavirin in HCV infection with genotype 2 or 3 for 14 weeks: a pilot study. *HEPATOLOGY* 2004;40:1260-1265.
117. Mangia A, Santoro R, Minerva N, Ricci GL, Carretta V, Persico M, et al. Peginterferon alfa-2b and ribavirin for 12 vs. 24 weeks in HCV genotype 2 or 3. *N Engl J Med* 2005;352:2609-2617.
118. von Wagner M, Huber M, Berg T, Hinrichsen H, Rasenack J, Heintges T, et al. Peginterferon-alpha-2a (40KD) and ribavirin for 16 or 24 weeks in patients with genotype 2 or 3 chronic hepatitis C. *Gastroenterology* 2005;129:522-527.
119. Yu ML, Dai CY, Huang JF, Hou NJ, Lee LP, Hsieh MY, et al. A randomized study of peginterferon and ribavirin for 16 versus 24 weeks in patients with genotype 2 chronic hepatitis C. *Gut* 2007;56:553-559.
120. Buti M, Sanchez-Avila F, Lurie Y, Stalgis C, Valdes A, Martell M, et al. Viral kinetics in genotype 1 chronic hepatitis C patients during therapy with 2 different doses of peginterferon alfa-2b plus ribavirin. *HEPATOLOGY* 2002;35:930-936.
121. Lindahl K, Stahle L, Bruchfeld A, Schvarcz R. High-dose ribavirin in combination with standard dose peginterferon for treatment of patients with chronic hepatitis C. *HEPATOLOGY* 2005;41:275-279.
122. Berg T, von Wagner M, Nasser S, Sarrazin C, Heintges T, Gerlach T, et al. Extended treatment duration for hepatitis C virus type 1: comparing 48 versus 72 weeks of peginterferon-alfa-2a plus ribavirin. *Gastroenterology* 2006;130:1086-1097.
123. Pearlman BL, Ehleben C, Saifce S. Treatment extension to 72 weeks of peginterferon and ribavirin in hepatitis c genotype 1-infected slow responders. *HEPATOLOGY* 2007;46:1688-1694.
124. Sanchez-Tapias JM, Diago M, Escartin P, Enriquez J, Romero-Gomez M, Barcena R, et al. Peginterferon-alfa2a plus ribavirin for 48 versus 72 weeks in patients with detectable hepatitis C virus RNA at week 4 of treatment. *Gastroenterology* 2006;131:451-460.
125. Soza A, Everhart JE, Ghany MG, Doo E, Heller T, Promrat K, et al. Neutropenia during combination therapy of interferon alfa and ribavirin for chronic hepatitis C. *HEPATOLOGY* 2002;36:1273-1279.
126. Afdhal NH, Dieterich DT, Pockros PJ, Schiff ER, Shiffman ML, Sulkowski MS, Wet al. Epoetin alfa maintains ribavirin dose in HCV-infected patients: a prospective, double-blind, randomized controlled study. *Gastroenterology* 2004;126:1302-1311.
127. Pockros PJ, Shiffman ML, Schiff ER, Sulkowski MS, Younossi Z, Dieterich DT, et al. Epoetin alfa improves quality of life in anemic HCV-infected patients receiving combination therapy. *HEPATOLOGY* 2004;40:1450-1458.
128. Shiffman ML, Salvatore J, Hubbard S, Price A, Sterling RK, Stravitz RT, et al. Treatment of chronic hepatitis C virus genotype 1 with peginterferon, ribavirin, and epoetin alpha. *HEPATOLOGY* 2007;46:371-379.
129. Del Rio RA, Post AB, Singer ME. Cost-effectiveness of hematologic growth factors for anemia occurring during hepatitis C combination therapy. *HEPATOLOGY* 2006;44:1598-1606.
130. Bennett CL, Silver SM, Djulbegovic B, Samaras AT, Blau CA, Gleason KJ, et al. Venous thromboembolism and mortality associated with recombinant erythropoietin and darbepoetin administration for the treatment of cancer-associated anemia. *Jama* 2008;299:914-924.
131. McHutchison JG, Dusheiko G, Shiffman ML, Rodriguez-Torres M, Sigal S, Bourliere M, Berg et al. Eltrombopag for thrombocytopenia in patients with cirrhosis associated with hepatitis C. *N Engl J Med* 2007;357:2227-2236.
132. Raison CL, Demetrashvili M, Capuron L, Miller AH. Neuropsychiatric adverse effects of interferon-alpha: recognition and management. *CNS Drugs* 2005;19:105-123.
133. Raison CL, Miller AH. The neuroimmunology of stress and depression. *Semin Clin Neuropsychiatry* 2001;6:277-294.
134. Cotler SJ, Wartelle CF, Larson AM, Gretch DR, Jensen DM, Carithers RL Jr. Pretreatment symptoms and dosing regimen predict side-effects of interferon therapy for hepatitis C. *J Viral Hepat* 2000;7:211-217.
135. Capuron L, Gumnick JF, Musselman DL, Lawson DH, Reemsnyder A, Nemeroff CB, et al. Neurobehavioral effects of interferon-alpha in cancer patients: phenomenology and paroxetine responsiveness of symptom dimensions. *Neuropsychopharmacology* 2002;26:643-652.
136. Czaja AJ, Freese DK. Diagnosis and treatment of autoimmune hepatitis. *HEPATOLOGY* 2002;36:479-497.
137. Zung WW. A Self-Rating Depression Scale. *Arch Gen Psychiatry* 1965;12:63-70.
138. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. *Arch Gen Psychiatry* 1961;4:561-571.
139. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry* 1979;134:382-389.
140. Radloff L. The CES-D Scale: a self-report depression scale for research in the general population. *J Applied Psychol Measurement* 1977;1:385-401.
141. Pradat P, Tillmann HL, Saulea S, Braconier JH, Saracco G, Thursz M, et al. Long-term follow-up of the hepatitis C HENCORE cohort: response to therapy and occurrence of liver-related complications. *J Viral Hepat* 2007;14:556-563.
142. Bruno S, Stroffolini T, Colombo M, Bollani S, Benvegna L, Mazzella G, et al. Sustained virological response to interferon-alpha is associated with improved outcome in HCV-related cirrhosis: a retrospective study. *HEPATOLOGY* 2007;45:579-587.
143. Veldt BJ, Heathcote EJ, Wedemeyer H, Reichen J, Hofmann WP, Zeuzem S, et al. Sustained virologic response and clinical outcomes in patients with chronic hepatitis C and advanced fibrosis. *Ann Intern Med* 2007;147:677-684.

144. Bruix J, Sherman M. Management of hepatocellular carcinoma. *HEPATOLOGY* 2005;42:1208-1236.
145. Cheruvattath R, Rosati MJ, Gautam M, Vargas HE, Rakela J, Balan V. Pegylated interferon and ribavirin failures: is retreatment an option? *Dig Dis Sci* 2007;52:732-736.
146. Cornberg M, Hadem J, Herrmann E, Schuppert F, Schmidt HH, Reiser M, et al. Treatment with daily consensus interferon (CIFN) plus ribavirin in non-responder patients with chronic hepatitis C: a randomized open-label pilot study. *J Hepatol* 2006;44:291-301.
147. Lee WM, Dienstag JL, Lindsay KL, Lok AS, Bonkovsky HL, Shiffman ML, et al. Evolution of the HALT-C Trial: pegylated interferon as maintenance therapy for chronic hepatitis C in previous interferon nonresponders. *Control Clin Trials* 2004;25:472-492.
148. Di Bisceglie AM, Shiffman ML, Everson GT, Lindsay KL, Everhart JE, Wright EC, et al. Prolonged therapy of advanced chronic hepatitis C with low-dose peginterferon. *N Engl J Med* 2008;359:2429-2441.
149. Taliani G, Gemignani G, Ferrari C, Aceti A, Bartolozzi D, Blanc PL, et al. Pegylated interferon alfa-2b plus ribavirin in the retreatment of interferon-ribavirin nonresponder patients. *Gastroenterology* 2006;130:1098-1106.
150. Shiffman ML, Di Bisceglie AM, Lindsay KL, Morishima C, Wright EC, Everson GT, et al. Peginterferon alfa-2a and ribavirin in patients with chronic hepatitis C who have failed prior treatment. *Gastroenterology* 2004;126:1015-1023; discussion 947.
151. Jacobson IM, Gonzalez SA, Ahmed F, Lebovics E, Min AD, Bodenheimer HC Jr, et al. A randomized trial of pegylated interferon alpha-2b plus ribavirin in the retreatment of chronic hepatitis C. *Am J Gastroenterol* 2005;100:2453-2462.
152. Pradat P, Alberti A, Poynard T, Esteban JI, Weiland O, Marcellin P, et al. Predictive value of ALT levels for histologic findings in chronic hepatitis C: a European collaborative study. *HEPATOLOGY* 2002;36:973-977.
153. Prieto M, Olaso V, Verdu C, Cordoba J, Gisbert C, Rayon M, et al. Does the healthy hepatitis C virus carrier state really exist? An analysis using polymerase chain reaction. *HEPATOLOGY* 1995;22:413-417.
154. Dufour DR, Lott JA, Nolte FS, Gretch DR, Koff RS, Seeff LB. Diagnosis and monitoring of hepatic injury. I. Performance characteristics of laboratory tests. *Clin Chem* 2000;46:2027-2049.
155. Brillanti S, Folli M, Gaiani S, Masci C, Miglioli M, Barbara L. Persistent hepatitis C viraemia without liver disease. *Lancet* 1993;341:464-465.
156. Prati D, Taioli E, Zanella A, Della Torre E, Butelli S, Del Vecchio E, et al. Updated definitions of healthy ranges for serum alanine aminotransferase levels. *Ann Intern Med* 2002;137:1-10.
157. Ahmed A, Keeffe EB. Chronic hepatitis C with normal aminotransferase levels. *Gastroenterology* 2004;126:1409-1415.
158. Nutt AK, Hassan HA, Lindsey J, Lamps LW, Raufman JP. Liver biopsy in the evaluation of patients with chronic hepatitis C who have repeatedly normal or near-normal serum alanine aminotransferase levels. *Am J Med* 2000;109:62-64.
159. Marcellin P. Hepatitis C: the clinical spectrum of the disease. *J Hepatol* 1999;31(Suppl 1):9-16.
160. Puoti C, Castellacci R, Montagnese F. Hepatitis C virus carriers with persistently normal aminotransferase levels: healthy people or true patients? *Dig Liver Dis* 2000;32:634-643.
161. Puoti C, Guido M, Mangia A, Persico M, Prati D. Clinical management of HCV carriers with normal aminotransferase levels. *Dig Liver Dis* 2003;35:362-369.
162. Puoti C, Magrini A, Stati T, Rigato P, Montagnese F, Rossi P, et al. Clinical, histological, and virological features of hepatitis C virus carriers with persistently normal or abnormal alanine transaminase levels. *HEPATOLOGY* 1997;26:1393-1398.
163. Arora S, O'Brien C, Zeuzem S, Shiffman ML, Diago M, Tran A, et al. Treatment of chronic hepatitis C patients with persistently normal alanine aminotransferase levels with the combination of peginterferon alpha-2a (40 kDa) plus ribavirin: impact on health-related quality of life. *J Gastroenterol Hepatol* 2006;21:406-412.
164. Bini EJ, Mehandru S. Sustained virological response rates and health-related quality of life after interferon and ribavirin therapy in patients with chronic hepatitis C virus infection and persistently normal alanine aminotransferase levels. *Aliment Pharmacol Ther* 2006;23:777-785.
165. Marcellin P, Asselah T, Boyer N. Fibrosis and disease progression in hepatitis C. *HEPATOLOGY* 2002;36(Suppl):S47-S56.
166. Jhaveri R, Grant W, Kauf TL, McHutchison J. The burden of hepatitis C virus infection in children: estimated direct medical costs over a 10-year period. *J Pediatr* 2006;148:353-358.
167. Hepatitis C virus infection. American Academy of Pediatrics. Committee on Infectious Diseases. *Pediatrics* 1998;101:481-485.
168. El-Kamary SS, Serwint JR, Joffe A, Santosham M, Duggan AK. Prevalence of hepatitis C virus infection in urban children. *J Pediatr* 2003;143:54-59.
169. Donahue JG, Munoz A, Ness PM, Brown DE Jr, Yawn DH, McAllister HA Jr, et al. The declining risk of post-transfusion hepatitis C virus infection. *N Engl J Med* 1992;327:369-373.
170. Kleinman S, Alter H, Busch M, Holland P, Tegtmeyer G, Nelles M, et al. Increased detection of hepatitis C virus (HCV)-infected blood donors by a multiple-antigen HCV enzyme immunoassay. *Transfusion* 1992;32:805-813.
171. Bortolotti F, Resti M, Giacchino R, Crivellaro C, Zancan L, Azzari C, et al. Changing epidemiologic pattern of chronic hepatitis C virus infection in Italian children. *J Pediatr* 1998;133:378-381.
172. Puro V, Girardi E, Ippolito G, Lo Presti E, Benedetto A, Zaniratti S, et al. Prevalence of hepatitis B and C viruses and human immunodeficiency virus infections in women of reproductive age. *Br J Obstet Gynaecol* 1992;99:598-600.
173. Airoldi J, Berghella V. Hepatitis C and pregnancy. *Obstet Gynecol Surv* 2006;61:666-672.
174. Pembrey L, Newell ML, Tovo PA. The management of HCV infected pregnant women and their children European paediatric HCV network. *J Hepatol* 2005;43:515-525.
175. Marcellin P, Bernuau J, Martinot-Peignoux M, Larzul D, Xu LZ, Tran S, et al. Prevalence of hepatitis C virus infection in asymptomatic anti-HIV1 negative pregnant women and their children. *Dig Dis Sci* 1993;38:2151-2155.
176. Roudot-Thoraval F, Pawlotsky JM, Thiers V, Deforges L, Girollet PP, Guillot F, et al. Lack of mother-to-infant transmission of hepatitis C virus in human immunodeficiency virus-seronegative women: a prospective study with hepatitis C virus RNA testing. *HEPATOLOGY* 1993;17:772-777.
177. Wejstal R, Widell A, Mansson AS, Hermodsson S, Norkrans G. Mother-to-infant transmission of hepatitis C virus. *Ann Intern Med* 1992;117:887-890.
178. Lam JP, McOmish F, Burns SM, Yap PL, Mok JY, Simmonds P. Infrequent vertical transmission of hepatitis C virus. *J Infect Dis* 1993;167:572-576.
179. Manzini P, Saracco G, Cerchier A, Riva C, Musso A, Ricotti E, et al. Human immunodeficiency virus infection as risk factor for mother-to-child hepatitis C virus transmission; persistence of anti-hepatitis C virus in children is associated with the mother's anti-hepatitis C virus immunoblotting pattern. *HEPATOLOGY* 1995;21:328-232.
180. Ohto H, Terazawa S, Sasaki N, Sasaki N, Hino K, Ishiwata C, et al. Transmission of hepatitis C virus from mothers to infants. The Vertical Transmission of Hepatitis C Virus Collaborative Study Group. *N Engl J Med* 1994;330:744-750.
181. European Paediatric Hepatitis C Virus Network. Effects of mode of delivery and infant feeding on the risk of mother-to-child transmission of hepatitis C virus. *Bjog* 2001;108:371-377.
182. Kumar RM, Shahul S. Role of breast-feeding in transmission of hepatitis C virus to infants of HCV-infected mothers. *J Hepatol* 1998;29:191-197.
183. Lin HH, Kao JH, Hsu HY, Ni YH, Chang MH, Huang SC, et al. Absence of infection in breast-fed infants born to hepatitis C virus-infected mothers. *J Pediatr* 1995;126:589-591.
184. Palomba E, Manzini P, Fiammengo P, Maderni P, Saracco G, Tovo PA. Natural history of perinatal hepatitis C virus infection. *Clin Infect Dis* 1996;23:47-50.

185. Polywka S, Pembrey L, Tovo PA, Newell ML. Accuracy of HCV-RNA PCR tests for diagnosis or exclusion of vertically acquired HCV infection. *J Med Virol* 2006;78:305-310.
186. Guido M, Ruge M, Jara P, Hierro L, Giacchino R, Larrauri J, et al. Chronic hepatitis C in children: the pathological and clinical spectrum. *Gastroenterology* 1998;115:1525-1529.
187. Yeung LT, To T, King SM, Roberts EA. Spontaneous clearance of childhood hepatitis C virus infection. *J Viral Hepat* 2007;14:797-805.
188. Camarero C, Ramos N, Moreno A, Asensio A, Mateos ML, Roldan B. Hepatitis C virus infection acquired in childhood. *Eur J Pediatr* 2008;167:219-224.
189. Hsu SC, Chang MH, Chen DS, Hsu HC, Lee CY. Non-A, non-B hepatitis in children: a clinical, histologic, and serologic study. *J Med Virol* 1991;35:1-6.
190. Bortolotti F, Vajro P, Cadrobbi P, Lepore L, Zancan L, Barbera C, et al. Cryptogenic chronic liver disease and hepatitis C virus infection in children. *J Hepatol* 1992;15:73-76.
191. Rumbo C, Fawaz RL, Emre SH, Suchy FJ, Kerkar N, Morotti RA, et al. Hepatitis C in children: a quaternary referral center perspective. *J Pediatr Gastroenterol Nutr* 2006;43:209-216.
192. D'Souza R, Glynn MJ, Ushiro-Lumb I, Feakins R, Domizio P, Mears L, et al. Prevalence of hepatitis C-related cirrhosis in elderly Asian patients infected in childhood. *Clin Gastroenterol Hepatol* 2005;3:910-917.
193. Jara P, Resti M, Hierro L, Giacchino R, Barbera C, Zancan L, et al. Chronic hepatitis C virus infection in childhood: clinical patterns and evolution in 224 white children. *Clin Infect Dis* 2003;36:275-280.
194. Goodman ZD, Makhlof HR, Liu L, Balistreri W, Gonzalez-Peralta RP, Haber B, et al. Pathology of chronic hepatitis C in children: liver biopsy findings in the Peds-C Trial. *HEPATOLOGY* 2008;47:836-843.
195. Mohan P, Colvin C, Glymph C, Chandra RR, Kleiner DE, Patel KM, et al. Clinical spectrum and histopathologic features of chronic hepatitis C infection in children. *J Pediatr* 2007;150:168-174, 174 e1.
196. Fujisawa T, Inui A, Ohkawa T, Komatsu H, Miyakawa Y, Onoue M. Response to interferon therapy in children with chronic hepatitis C. *J Pediatr* 1995;127:660-662.
197. Bortolotti F, Giacchino R, Vajro P, Barbera C, Crivellaro C, Alberti A, et al. Recombinant interferon-alpha therapy in children with chronic hepatitis C. *HEPATOLOGY* 1995;22:1623-1627.
198. Marcellini M, Kondili LA, Comparcola D, Spada E, Sartorelli MR, Palumbo M, et al. High dosage alpha-interferon for treatment of children and young adults with chronic hepatitis C disease. *Pediatr Infect Dis J* 1997;16:1049-1053.
199. Gonzalez-Peralta RP, Kelly DA, Haber B, Molleston J, Murray KF, Jonas MM, et al. Interferon alpha-2b in combination with ribavirin for the treatment of chronic hepatitis C in children: efficacy, safety, and pharmacokinetics. *HEPATOLOGY* 2005;42:1010-1018.
200. Wirth S, Lang T, Gehring S, Gerner P. Recombinant alpha-interferon plus ribavirin therapy in children and adolescents with chronic hepatitis C. *HEPATOLOGY* 2002;36:1280-1284.
201. Christensson B, Wiebe T, Akesson A, Widell A. Interferon-alpha and ribavirin treatment of hepatitis C in children with malignancy in remission. *Clin Infect Dis* 2000;30:585-586.
202. Wirth S, Pieper-Boustani H, Lang T, Ballauff A, Kullmer U, Gerner P, et al. Peginterferon alpha-2b plus ribavirin treatment in children and adolescents with chronic hepatitis C. *HEPATOLOGY* 2005;41:1013-1018.
203. Jara P, Hierro L, de la Vega A, Diaz C, Camarena C, Frauca E, et al. Efficacy and safety of peginterferon-alpha2b and ribavirin combination therapy in children with chronic hepatitis C infection. *Pediatr Infect Dis J* 2008;27:142-148.
204. Sherman KE, Rouster SD, Chung RT, Rajcic N. Hepatitis C Virus prevalence among patients infected with Human Immunodeficiency Virus: a cross-sectional analysis of the US adult AIDS Clinical Trials Group. *Clin Infect Dis* 2002;34:831-837.
205. Bica I, McGovern B, Dhar R, Stone D, McGowan K, Scheib R, et al. Increasing mortality due to end-stage liver disease in patients with human immunodeficiency virus infection. *Clin Infect Dis* 2001;32:492-497.
206. Palella FJ Jr, Delaney KM, Moorman AC, Loveless MO, Fuhrer J, Satten GA, et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators. *N Engl J Med* 1998;338:853-860.
207. Weber R, Sabin CA, Friis-Moller N, Reiss P, El-Sadr WM, Kirk O, et al. Liver-related deaths in persons infected with the human immunodeficiency virus: the D:A:D study. *Arch Intern Med* 2006;166:1632-1641.
208. Bonacini M, Lin HJ, Hollinger FB. Effect of coexisting HIV-1 infection on the diagnosis and evaluation of hepatitis C virus. *J Acquir Immune Defic Syndr* 2001;26:340-344.
209. Marcellin P, Martinot-Peignoux M, Elias A, Branger M, Courtois F, Level R, et al. Hepatitis C virus (HCV) viremia in human immunodeficiency virus-seronegative and -seropositive patients with indeterminate HCV recombinant immunoblot assay. *J Infect Dis* 1994;170:433-435.
210. Graham CS, Baden LR, Yu E, Mrus JM, Carnie J, Heeren T, et al. Influence of human immunodeficiency virus infection on the course of hepatitis C virus infection: a meta-analysis. *Clin Infect Dis* 2001;33:562-569.
211. Sulkowski MS. The HIV-coinfected patient: managing viral hepatitis. *J Acquir Immune Defic Syndr* 2007;45 Suppl 2:S36-S37.
212. Sulkowski MS, Thomas DL, Chaisson RE, Moore RD. Hepatotoxicity associated with antiretroviral therapy in adults infected with human immunodeficiency virus and the role of hepatitis C or B virus infection. *Jama* 2000;283:74-80.
213. Labarga P, Soriano V, Vispo ME, Pinilla J, Martin-Carbonero L, Castellares C, et al. Hepatotoxicity of Antiretroviral Drugs Is Reduced after Successful Treatment of Chronic Hepatitis C in HIV-Infected Patients. *J Infect Dis* 2007;196:670-676.
214. Soriano V, Garcia-Samaniego J, Bravo R, Gonzalez J, Castro A, Castilla J, et al. Interferon alpha for the treatment of chronic hepatitis C in patients infected with human immunodeficiency virus. Hepatitis-HIV Spanish Study Group. *Clin Infect Dis* 1996;23:585-591.
215. Laguno M, Murillas J, Blanco JL, Martinez E, Miquel R, Sanchez-Tapias JM, et al. Peginterferon alpha-2b plus ribavirin compared with interferon alpha-2b plus ribavirin for treatment of HIV/HCV co-infected patients. *Aids* 2004;18:F27-F36.
216. Chung RT, Andersen J, Volberding P, Robbins GK, Liu T, Sherman KE, et al. Peginterferon Alfa-2a plus ribavirin versus interferon alfa-2a plus ribavirin for chronic hepatitis C in HIV-coinfected persons. *N Engl J Med* 2004;351:451-459.
217. Torriani FJ, Rodriguez-Torres M, Rockstroh JK, Lissen E, Gonzalez-Garcia J, Lazzarin A, et al. Peginterferon Alfa-2a plus ribavirin for chronic hepatitis C virus infection in HIV-infected patients. *N Engl J Med* 2004;351:438-450.
218. Carrat F, Bani-Sadr F, Pol S, Rosenthal E, Lunel-Fabiani F, Benzekri A, et al. Pegylated interferon alpha-2b vs standard interferon alpha-2b, plus ribavirin, for chronic hepatitis C in HIV-infected patients: a randomized controlled trial. *Jama* 2004;292:2839-2848.
219. Soriano V, Bravo R, Garcia-Samaniego J, Castilla J, Gonzalez J, Castro A, et al. Relapses of chronic hepatitis C in HIV-infected patients who responded to interferon therapy. Hepatitis/HIV Spanish Study Group. *Aids* 1997;11:400-401.
220. Mauss S, Valenti W, DePamphilis J, Duff F, Cupelli L, Passe S, et al. Risk factors for hepatic decompensation in patients with HIV/HCV coinfection and liver cirrhosis during interferon-based therapy. *Aids* 2004;18:F21-F25.
221. Moore RD. Human immunodeficiency virus infection, anemia, and survival. *Clin Infect Dis* 1999;29:44-49.
222. Alvarez D, Dieterich DT, Brau N, Moorehead L, Ball L, Sulkowski MS. Zidovudine use but not weight-based ribavirin dosing impacts anaemia during HCV treatment in HIV-infected persons. *J Viral Hepat* 2006;13:683-689.
223. Hoggard PG, Kewn S, Barry MG, Khoo SH, Back DJ. Effects of drugs on 2',3'-dideoxy-2',3'-dideohydrothymidine phosphorylation in vitro. *Antimicrob Agents Chemother* 1997;41:1231-1236.
224. Lafeuillade A, Hittinger G, Chadapaud S. Increased mitochondrial toxicity with ribavirin in HIV/HCV coinfection. *Lancet* 2001;357:280-281.

225. Salmon-Ceron D, Chauvelot-Moachon L, Abad S, Silbermann B, Sogni P. Mitochondrial toxic effects and ribavirin. *Lancet* 2001;357:1803-1804.
226. Bristol Myers Squibb. Patient Information. Packageinserts.bms.com/pi/pi_videx_ec.pdf. 2003.
227. Zylberberg H, Benhamou Y, Lagneaux JL, Landau A, Chaix ML, Fontaine H, et al. Safety and efficacy of interferon-ribavirin combination therapy in HCV-HIV coinfecting subjects: an early report. *Gut* 2000;47:694-697.
228. Landau A, Batisse D, Piketty C, Jian R, Kazatchkine MD. Lack of interference between ribavirin and nucleosidic analogues in HIV/HCV coinfecting individuals undergoing concomitant antiretroviral and anti-HCV combination therapy. *Aids* 2000;14:1857-1858.
229. Fattovich G, Giustina G, Favarato S, Ruol A. A survey of adverse events in 11,241 patients with chronic viral hepatitis treated with alpha interferon. *J Hepatol* 1996;24:38-47.
230. Lane HC, Davey V, Kovacs JA, Feinberg J, Metcalf JA, Herpin B, et al. Interferon-alpha in patients with asymptomatic human immunodeficiency virus (HIV) infection. A randomized, placebo-controlled trial. *Ann Intern Med* 1990;112:805-811.
231. Valerio L, Yazdanpanah Y, Poizot-Martin I, Rosenthal E, Marimoutou C, Gastaut JA, et al. Baseline CD4 cell count and outcome of pegylated interferon plus ribavirin therapy in HIV/hepatitis C virus-coinfecting patients. *J Acquir Immune Defic Syndr* 2008;47:50-55.
232. Opravil M, Sasadeusz J, Cooper DA, Rockstroh JK, Clumeck N, Clotet B, et al. Effect of baseline CD4 cell count on the efficacy and safety of peginterferon Alfa-2a (40KD) plus ribavirin in patients with HIV/hepatitis C virus coinfection. *J Acquir Immune Defic Syndr* 2008;47:36-49.
233. Roland ME, Havlir DV. Responding to organ failure in HIV-infected patients. *N Engl J Med* 2003;348:2279-2281.
234. Duclos-Vallee JC, Feray C, Sebah M, Teicher E, Roque-Afonso AM, Roche B, et al. Survival and recurrence of hepatitis C after liver transplantation in patients coinfecting with human immunodeficiency virus and hepatitis C virus. *HEPATOLOGY* 2008;47:407-417.
235. Fissell RB, Bragg-Gresham JL, Woods JD, Jadoul M, Gillespie B, Hedderwick SA, et al. Patterns of hepatitis C prevalence and seroconversion in hemodialysis units from three continents: the DOPPS. *Kidney Int* 2004;65:2335-2342.
236. Fabrizi F, Poordad FF, Martin P. Hepatitis C infection and the patient with end-stage renal disease. *HEPATOLOGY* 2002;36:3-10.
237. Tokars JI, Miller ER, Alter MJ, Arduino MJ. National surveillance of dialysis-associated diseases in the United States, 1997. *Semin Dial* 2000;13:75-85.
238. Saha D, Agarwal SK. Hepatitis and HIV infection during haemodialysis. *J Indian Med Assoc* 2001;99:194-9, 203, 213.
239. Moreira RC, Lemos MF, Longui CA, Granato C. Hepatitis C and hemodialysis: a review. *Braz J Infect Dis* 2005;9:269-275.
240. Recommendations for preventing transmission of infections among chronic hemodialysis patients. *MMWR Recomm Rep* 2001;50:1-43.
241. Tang S, Lai KN. Chronic viral hepatitis in hemodialysis patients. *Hemodial Int* 2005;9:169-179.
242. Jadoul M, Cornu C, van Ypersele de Strihou C. Universal precautions prevent hepatitis C virus transmission: a 54 month follow-up of the Belgian Multicenter Study. The Universitaires Cliniques St-Luc (UCL) Collaborative Group. *Kidney Int* 1998;53:1022-1025.
243. D'Amico G. Renal involvement in hepatitis C infection: cryoglobulinemic glomerulonephritis. *Kidney Int* 1998;54:650-671.
244. Sabry AA, Sobh MA, Irving WL, Grabowska A, Wagner BE, Fox S, et al. A comprehensive study of the association between hepatitis C virus and glomerulopathy. *Nephrol Dial Transplant* 2002;17:239-245.
245. Dore MP, Fattovich G, Sepulveda AR, Realdi G. Cryoglobulinemia related to hepatitis C virus infection. *Dig Dis Sci* 2007;52:897-907.
246. Roccatello D, Fornasiero A, Giachino O, Rossi D, Beltrame A, Banfi G, et al. Multicenter study on hepatitis C virus-related cryoglobulinemic glomerulonephritis. *Am J Kidney Dis* 2007;49:69-82.
247. Agnello V, Chung RT, Kaplan LM. A role for hepatitis C virus infection in type II cryoglobulinemia. *N Engl J Med* 1992;327:1490-1495.
248. Markowitz GS, Cheng JT, Colvin RB, Trebbin WM, D'Agati VD. Hepatitis C viral infection is associated with fibrillary glomerulonephritis and immunotactoid glomerulopathy. *J Am Soc Nephrol* 1998;9:2244-2252.
249. Marcelli D, Stannard D, Conte F, Held PJ, Locatelli F, Port FK. ESRD patient mortality with adjustment for comorbid conditions in Lombardy (Italy) versus the United States. *Kidney Int* 1996;50:1013-1018.
250. Maisonneuve P, Agodoa L, Gellert R, Stewart JH, Bucciante G, Lowenfels AB, et al. Cancer in patients on dialysis for end-stage renal disease: an international collaborative study. *Lancet* 1999;354:93-99.
251. Nakayama E, Akiba T, Marumo F, Sato C. Prognosis of anti-hepatitis C virus antibody-positive patients on regular hemodialysis therapy. *J Am Soc Nephrol* 2000;11:1896-1902.
252. Lee WC, Shu KH, Cheng CH, Wu MJ, Chen CH, Lian JC. Long-term impact of hepatitis B, C virus infection on renal transplantation. *Am J Nephrol* 2001;21:300-306.
253. Bruchfeld A, Wilczek H, Elinder CG. Hepatitis C infection, time in renal-replacement therapy, and outcome after kidney transplantation. *Transplantation* 2004;78:745-750.
254. Aroldi A, Lampertico P, Montagnino G, Passerini P, Villa M, Campise MR, et al. Natural history of hepatitis B and C in renal allograft recipients. *Transplantation* 2005;79:1132-1136.
255. Bloom RD, Rao V, Weng F, Grossman RA, Cohen D, Mange KC. Association of hepatitis C with posttransplant diabetes in renal transplant patients on tacrolimus. *J Am Soc Nephrol* 2002;13:1374-1380.
256. Kamar N, Mariat C, Delahousse M, Dantal J, Najjar AA, Cassuto E, et al. Diabetes mellitus after kidney transplantation: a French multicentre observational study. *Nephrol Dial Transplant* 2007;22:1986-1993.
257. Fabrizi F, Martin P, Dixit V, Bunnapradist S, Kanwal F, Dulai G. Post-transplant diabetes mellitus and HCV seropositive status after renal transplantation: meta-analysis of clinical studies. *Am J Transplant* 2005;5:2433-2440.
258. Roth D, Cirocco R, Zucker K, Ruiz P, Viciano A, Burke G, et al. De novo membranoproliferative glomerulonephritis in hepatitis C virus-infected renal allograft recipients. *Transplantation* 1995;59:1676-1682.
259. Floege J. Recurrent glomerulonephritis following renal transplantation: an update. *Nephrol Dial Transplant* 2003;18:1260-1265.
260. Choy BY, Chan TM, Lai KN. Recurrent glomerulonephritis after kidney transplantation. *Am J Transplant* 2006;6:2535-2542.
261. Levey AS, Coresh J, Balk E, Kausz AT, Levin A, Steffes MW, et al. National Kidney Foundation practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Ann Intern Med* 2003;139:137-147.
262. Guh JY, Lai YH, Yang CY, Chen SC, Chuang WL, Hsu TC, et al. Impact of decreased serum transaminase levels on the evaluation of viral hepatitis in hemodialysis patients. *Nephron* 1995;69:459-465.
263. Fabrizi F, Lunghi G, Finazzi S, Colucci P, Pagano A, Ponticelli C, et al. Decreased serum aminotransferase activity in patients with chronic renal failure: impact on the detection of viral hepatitis. *Am J Kidney Dis* 2001;38:1009-1015.
264. Perez RM, Ferreira AS, Medina-Pestana JO, Lanzoni VP, Silva AE, Ferraz ML. Is alanine aminotransferase a good marker of histologic hepatic damage in renal transplant patients with hepatitis C virus infection? *Clin Transplant* 2005;19:622-625.
265. Contreras AM, Ruiz I, Polanco-Cruz G, Monteon FJ, Celis A, Vazquez G, et al. End-stage renal disease and hepatitis C infection: comparison of alanine aminotransferase levels and liver histology in patients with and without renal damage. *Ann Hepatol* 2007;6:48-54.
266. Brophy DF, Martin EJ, Carr SL, Kirschbaum B, Carr ME Jr. The effect of uremia on platelet contractile force, clot elastic modulus and bleeding time in hemodialysis patients. *Thromb Res* 2007;119:723-729.
267. Kaw D, Malhotra D. Platelet dysfunction and end-stage renal disease. *Semin Dial* 2006;19:317-322.
268. Weigert AL, Schafer AI. Uremic bleeding: pathogenesis and therapy. *Am J Med Sci* 1998;316:94-104.
269. Lemos LB, Perez RM, Lemos MM, Lanzoni VP, Draibe SA, Silva IS, et al. Hepatitis C in chronic kidney disease: predialysis patients present more

- severe histological liver injury than hemodialysis patients? *Am J Nephrol* 2007;27:191-196.
270. Martin P, Carter D, Fabrizi F, Dixit V, Conrad AJ, Artinian L, et al. Histopathological features of hepatitis C in renal transplant candidates [see comment]. *Transplantation* 2000;69:1479-1484.
 271. Furusyo N, Hayashi J, Kanamoto-Tanaka Y, Ariyama I, Etoh Y, Shigematsu M, et al. Liver damage in hemodialysis patients with hepatitis C virus viremia: a prospective 10-year study. *Dig Dis Sci* 2000;45:2221-2228.
 272. Rockey D, Caldwell AH, Goodman ZD, Nelson RC, Smith AD. AASLD Position Paper: Liver Biopsy. *HEPATOLOGY* 2009;49:1017-1044.
 273. Kidney disease: improving global outcomes (KDIGO). *Kidney Int Suppl* 2008:S1-S99.
 274. Bocci V, Pacini A, Muscettola M, Paulesu L, Pessina GP, Santiano M, et al. Renal filtration, absorption and catabolism of human alpha interferon. *J Interferon Res* 1981;1:347-352.
 275. Bino T, Madar Z, Gertler A, Rosenberg H. The kidney is the main site of interferon degradation. *J Interferon Res* 1982;2:301-308.
 276. Kramer TH, Gaar GG, Ray CG, Minnich L, Copeland JG, Connor JD. Hemodialysis clearance of intravenously administered ribavirin. *Antimicrob Agents Chemother* 1990;34:489-490.
 277. Glue P. The clinical pharmacology of ribavirin. *Semin Liver Dis* 1999;19 Suppl 1:17-24.
 278. Uchihara M, Izumi N, Sakai Y, Yauchi T, Miyake S, Sakai T, et al. Interferon therapy for chronic hepatitis C in hemodialysis patients: increased serum levels of interferon. *Nephron* 1998;80:51-56.
 279. Rostaing L, Chatelut E, Payen JL, Izopet J, Thalamas C, Ton-That H, et al. Pharmacokinetics of alphaIFN-2b in chronic hepatitis C virus patients undergoing chronic hemodialysis or with normal renal function: clinical implications. *J Am Soc Nephrol* 1998;9:2344-2348.
 280. Glue P, Fang JW, Rouzier-Panis R, Raffanel C, Sabo R, Gupta SK, et al. Pegylated interferon-alpha2b: pharmacokinetics, pharmacodynamics, safety, and preliminary efficacy data. Hepatitis C Intervention Therapy Group. *Clin Pharmacol Ther* 2000;68:556-567.
 281. Gupta SK, Pittenger AL, Swan SK, Marbury TC, Tobillo E, Batra V, et al. Single-dose pharmacokinetics and safety of pegylated interferon-alpha2b in patients with chronic renal dysfunction. *J Clin Pharmacol* 2002;42:1109-1115.
 282. Bruchfeld A, Lindahl K, Reichard O, Carlsson T, Schvarcz R. Pegylated interferon and ribavirin treatment for hepatitis C in haemodialysis patients. *J Viral Hepat* 2006;13:316-321.
 283. Bruchfeld A, Lindahl K, Stahle L, Soderberg M, Schvarcz R. Interferon and ribavirin treatment in patients with hepatitis C-associated renal disease and renal insufficiency. *Nephrol Dial Transplant* 2003;18:1573-1580.
 284. Meyers CM, Seeff LB, Stehman-Breen CO, Hoofnagle JH. Hepatitis C and renal disease: an update. *Am J Kidney Dis* 2003;42:631-657.
 285. Fabrizi F, Dulai G, Dixit V, Bunnapradist S, Martin P. Meta-analysis: interferon for the treatment of chronic hepatitis C in dialysis patients. *Aliment Pharmacol Ther* 2003;18:1071-1081.
 286. Russo MW, Goldsweig CD, Jacobson IM, Brown RS Jr. Interferon monotherapy for dialysis patients with chronic hepatitis C: an analysis of the literature on efficacy and safety. *Am J Gastroenterol* 2003;98:1610-1615.
 287. Rivera M, Gentil MA, Sayago M, Gonzalez Roncero F, Trigo C, Algarra G, et al. Treatment of hepatitis C virus with interferon in hemodialysis patients awaiting kidney transplant. *Transplant Proc* 2005;37:1424-1425.
 288. Rocha CM, Perez RM, Ferreira AP, Carvalho-Filho RJ, Pace FH, Silva IS, et al. Efficacy and tolerance of interferon-alpha in the treatment of chronic hepatitis C in end-stage renal disease patients on hemodialysis. *Liver Int* 2006;26:305-310.
 289. Kalia H, Lopez PM, Martin P. Treatment of HCV in patients with renal failure. *Arch Med Res* 2007;38:628-633.
 290. Tan AC, Brouwer JT, Glue P, van Leusen R, Kauffmann RH, Schalm SW, et al. Safety of interferon and ribavirin therapy in haemodialysis patients with chronic hepatitis C: results of a pilot study. *Nephrol Dial Transplant* 2001;16:193-195.
 291. Mousa DH, Abdalla AH, Al-Shoail G, Al-Sulaiman MH, Al-Hawas FA, Al-Khader AA. Alpha-interferon with ribavirin in the treatment of hemodialysis patients with hepatitis C. *Transplant Proc* 2004;36:1831-1834.
 292. Chan TM, Ho SK, Tang CS, Tse KC, Lam MF, Lai KN, et al. Pilot study of pegylated interferon-alpha 2a in dialysis patients with chronic hepatitis C virus infection. *Nephrology (Carlton)* 2007;12:11-17.
 293. Sporea I, Popescu A, Sirli R, Golea O, Torolici C, Danila M, et al. Pegylated-interferon alpha 2a treatment for chronic hepatitis C in patients on chronic haemodialysis. *World J Gastroenterol* 2006;12:4191-4194.
 294. Kokoglu OF, Ucmak H, Hosoglu S, Cetinkaya A, Kantarceken B, Buyukbese MA, et al. Efficacy and tolerability of pegylated-interferon alpha-2a in hemodialysis patients with chronic hepatitis C. *J Gastroenterol Hepatol* 2006;21:575-580.
 295. Covic A, Maftai ID, Mardare NG, Ionita-Radu F, Totolici C, Tuta L, et al. Analysis of safety and efficacy of pegylated-interferon alpha-2a in hepatitis C virus positive hemodialysis patients: results from a large, multicenter audit. *J Nephrol* 2006;19:794-801.
 296. Russo MW, Ghalib R, Sigal S, Joshi V. Randomized trial of pegylated interferon alpha-2b monotherapy in haemodialysis patients with chronic hepatitis C. *Nephrol Dial Transplant* 2006;21:437-443.
 297. Rendina M, Schena A, Castellaneta NM, Losito F, Amoruso AC, Stallone G, et al. The treatment of chronic hepatitis C with peginterferon alpha-2a (40 kDa) plus ribavirin in haemodialysed patients awaiting renal transplant. *J Hepatol* 2007;46:768-774.
 298. Wolfe RA, Ashby VB, Milford EL, Ojo AO, Ettenger RE, Agodoa LY, et al. Comparison of mortality in all patients on dialysis, patients on dialysis awaiting transplantation, and recipients of a first cadaveric transplant. *N Engl J Med* 1999;341:1725-1730.
 299. Campistol JM, Esforzado N, Martinez J, Rosello L, Veciana L, Modol J, et al. Efficacy and tolerance of interferon-alpha(2b) in the treatment of chronic hepatitis C virus infection in haemodialysis patients. Pre- and post-renal transplantation assessment. *Nephrol Dial Transplant* 1999;14:2704-2709.
 300. Carriero D, Fabrizi F, Uriel AJ, Park J, Martin P, Dieterich DT. Treatment of dialysis patients with chronic hepatitis C using pegylated interferon and low-dose ribavirin. *Int J Artif Organs* 2008;31:295-302.
 301. Rostaing L, Izopet J, Baron E, Duffaut M, Puel J, Durand D. Treatment of chronic hepatitis C with recombinant interferon alpha in kidney transplant recipients. *Transplantation* 1995;59:1426-1431.
 302. Tang S, Cheng IK, Leung VK, Kuok UI, Tang AW, Wing Ho Y, et al. Successful treatment of hepatitis C after kidney transplantation with combined interferon alpha-2b and ribavirin. *J Hepatol* 2003;39:875-878.
 303. Shu KH, Lan JL, Wu MJ, Cheng CH, Chen CH, Lee WC, et al. Ultralow-dose alpha-interferon plus ribavirin for the treatment of active hepatitis C in renal transplant recipients. *Transplantation* 2004;77:1894-1896.
 304. Sharma RK, Bansal SB, Gupta A, Gulati S, Kumar A, Prasad N. Chronic hepatitis C virus infection in renal transplant: treatment and outcome. *Clin Transplant* 2006;20:677-683.
 305. Fontaine H, Valler-Pichard A, Equi-Andrade C, Nalpas B, Verkarre V, Chaix ML, et al. Histopathologic efficacy of ribavirin monotherapy in kidney allograft recipients with chronic hepatitis C. *Transplantation* 2004;78:853-857.
 306. Kamar N, Ribes D, Izopet J, Rostaing L. Treatment of hepatitis C virus infection (HCV) after renal transplantation: implications for HCV-positive dialysis patients awaiting a kidney transplant. *Transplantation* 2006;82:853-856.
 307. Toth CM, Pascual M, Chung RT, Graeme-Cook F, Dienstag JL, Bhan AK, et al. Hepatitis C virus-associated fibrosing cholestatic hepatitis after renal transplantation: response to interferon-alpha therapy. *Transplantation* 1998;66:1254-1258.
 308. Cid MC, Hernandez-Rodriguez J, Robert J, del Rio A, Casademont J, Coll-Vinent B, et al. Interferon-alpha may exacerbate cryoglobulinemia-

- related ischemic manifestations: an adverse effect potentially related to its anti-angiogenic activity. *Arthritis Rheum* 1999;42:1051-1055.
309. Suzuki T, Yonemura K, Miyaji T, Suzuki H, Takahira R, Fujigaki Y, et al. Progressive renal failure and blindness due to retinal hemorrhage after interferon therapy for hepatitis C virus-associated membranoproliferative glomerulonephritis. *Intern Med* 2001;40:708-712.
 310. Kamar N, Rostaing L, Alric L. Treatment of hepatitis C-virus-related glomerulonephritis. *Kidney Int* 2006;69:436-439.
 311. Basse G, Ribes D, Kamar N, Mehrenberger M, Esposito L, Guitard J, et al. Rituximab therapy for de novo mixed cryoglobulinemia in renal transplant patients. *Transplantation* 2005;80:1560-1564.
 312. Garini G, Allegri L, Vaglio A, Buzio C. Hepatitis C virus-related cryoglobulinemia and glomerulonephritis: pathogenesis and therapeutic strategies. *Ann Ital Med Int* 2005;20:71-80.
 313. Misiani R, Bellavita P, Fenili D, Vicari O, Marchesi D, Sironi PL, et al. Interferon alfa-2a therapy in cryoglobulinemia associated with hepatitis C virus. *N Engl J Med* 1994;330:751-756.
 314. Cresta P, Musset L, Cacoub P, Frangeul L, Vitour D, Poynard T, et al. Response to interferon alpha treatment and disappearance of cryoglobulinaemia in patients infected by hepatitis C virus. *Gut* 1999;45:122-128.
 315. Garini G, Allegri L, Carnevali L, Catellani W, Manganelli P, Buzio C. Interferon-alpha in combination with ribavirin as initial treatment for hepatitis C virus-associated cryoglobulinemic membranoproliferative glomerulonephritis. *Am J Kidney Dis* 2001;38:E35.
 316. Rossi P, Bertani T, Baio P, Caldara R, Luliri P, Tengattini F, et al. Hepatitis C virus-related cryoglobulinemic glomerulonephritis: long-term remission after antiviral therapy. *Kidney Int* 2003;63:2236-2241.
 317. Mazzaro C, Zorat F, Caizzi M, Donada C, Di Gennaro G, Maso LD, et al. Treatment with peg-interferon alfa-2b and ribavirin of hepatitis C virus-associated mixed cryoglobulinemia: a pilot study. *J Hepatol* 2005;42:632-638.
 318. Cacoub P, Saadoun D, Limal N, Sene D, Lidove O, Piette JC. PEGylated interferon alfa-2b and ribavirin treatment in patients with hepatitis C virus-related systemic vasculitis. *Arthritis Rheum* 2005;52:911-915.
 319. Saadoun D, Resche-Rigon M, Thibault V, Piette JC, Cacoub P. Antiviral therapy for hepatitis C virus-associated mixed cryoglobulinemia vasculitis: a long-term followup study. *Arthritis Rheum* 2006;54:3696-706.
 320. El-Serag HB. Hepatocellular carcinoma: recent trends in the United States. *Gastroenterology* 2004;127:S27-S34.
 321. Muir AJ, Bornstein JD, Killenberg PG. Peginterferon alfa-2b and ribavirin for the treatment of chronic hepatitis C in blacks and non-Hispanic whites. *N Engl J Med* 2004;350:2265-2271.
 322. Conjeevaram HS, Fried MW, Jeffers LJ, Terrault NA, Wiley-Lucas TE, Afdhal N, et al. Peginterferon and ribavirin treatment in African American and Caucasian American patients with hepatitis C genotype 1. *Gastroenterology* 2006;131:470-477.
 323. Jacobson IM, Brown RS Jr, McCone J, Black M, Albert C, Dragutsky MS, et al. Impact of weight-based ribavirin with peginterferon alfa-2b in African Americans with hepatitis C virus genotype 1. *HEPATOLOGY* 2007;46:982-990.
 324. Shiffman ML, Mihas AA, Millwala F, Sterling RK, Luketic VA, Stravitz RT, et al. Treatment of chronic hepatitis C virus in African Americans with genotypes 2 and 3. *Am J Gastroenterol* 2007;102:761-766.
 325. Jeffers LJ, Cassidy W, Howell CD, Hu S, Reddy KR. Peginterferon alfa-2a (40 kd) and ribavirin for black American patients with chronic HCV genotype 1. *HEPATOLOGY* 2004;39:1702-1708.
 326. Heathcote EJ, Shiffman ML, Cooksley WG, Dusheiko GM, Lee SS, Balart L, et al. Peginterferon alfa-2a in patients with chronic hepatitis C and cirrhosis. *N Engl J Med* 2000;343:1673-1680.
 327. Helbling B, Jochum W, Stamenic I, Knopfli M, Cerny A, Borovicka J, et al. HCV-related advanced fibrosis/cirrhosis: randomized controlled trial of pegylated interferon alpha-2a and ribavirin. *J Viral Hepat* 2006;13:762-769.
 328. Berenguer M, Ferrell L, Watson J, Prieto M, Kim M, Rayon M, et al. HCV-related fibrosis progression following liver transplantation: increase in recent years. *J Hepatol* 2000;32:673-684.
 329. Sanchez-Fueyo A, Restrepo JC, Quinto L, Bruguera M, Grande L, Sanchez-Tapias JM, et al. Impact of the recurrence of hepatitis C virus infection after liver transplantation on the long-term viability of the graft. *Transplantation* 2002;73:56-63.
 330. Crippin JS, McCashland T, Terrault N, Sheiner P, Charlton MR. A pilot study of the tolerability and efficacy of antiviral therapy in hepatitis C virus-infected patients awaiting liver transplantation. *Liver Transpl* 2002;8:350-355.
 331. Forns X, Garcia-Retortillo M, Serrano T, Feliu A, Suarez F, de la Mata M, et al. Antiviral therapy of patients with decompensated cirrhosis to prevent recurrence of hepatitis C after liver transplantation. *J Hepatol* 2003;39:389-396.
 332. Thomas RM, Brems JJ, Guzman-Hartman G, Yong S, Cavaliere P, Van Thiel DH. Infection with chronic hepatitis C virus and liver transplantation: a role for interferon therapy before transplantation. *Liver Transpl* 2003;9:905-915.
 333. Everson GT, Trotter J, Forman L, Kugelmas M, Halprin A, Fey B, et al. Treatment of advanced hepatitis C with a low accelerating dosage regimen of antiviral therapy. *HEPATOLOGY* 2005;42:255-262.
 334. Iacobellis A, Siciliano M, Perri F, Annicchiarico BE, Leandro G, Caruso N, et al. Peginterferon alfa-2b and ribavirin in patients with hepatitis C virus and decompensated cirrhosis: a controlled study. *J Hepatol* 2007;46:206-212.
 335. Wright TL, Donegan E, Hsu HH, Ferrell L, Lake JR, Kim M, et al. Recurrent and acquired hepatitis C viral infection in liver transplant recipients. *Gastroenterology* 1992;103:317-322.
 336. Pereira BJ, Natov SN, Bouthot BA, Murthy BV, Ruthazer R, Schmid CH, et al. Effects of hepatitis C infection and renal transplantation on survival in end-stage renal disease. The New England Organ Bank Hepatitis C Study Group. *Kidney Int* 1998;53:1374-1381.
 337. Gudmundsson GS, Malinowska K, Robinson JA, Pisani BA, Mendez JC, Foy BK, et al. Five-year follow-up of hepatitis C-naive heart transplant recipients who received hepatitis C-positive donor hearts. *Transplant Proc* 2003;35:1536-1538.
 338. Lunel F, Cadranet JF, Rosenheim M, Dorent R, Di-Martino V, Payan C, et al. Hepatitis virus infections in heart transplant recipients: epidemiology, natural history, characteristics, and impact on survival. *Gastroenterology* 2000;119:1064-1074.
 339. Marelli D, Bresson J, Laks H, Kubak B, Fonarow G, Tsai FC, et al. Hepatitis C-positive donors in heart transplantation. *Am J Transplant* 2002;2:443-447.
 340. Haji SA, Starling RC, Avery RK, Mawhorter S, Tuzcu EM, Schoenhagen P, et al. Donor hepatitis-C seropositivity is an independent risk factor for the development of accelerated coronary vasculopathy and predicts outcome after cardiac transplantation. *J Heart Lung Transplant* 2004;23:277-283.
 341. Sahi H, Zein NN, Mehta AC, Blazey HC, Meyer KH, Budev M. Outcomes after lung transplantation in patients with chronic hepatitis C virus infection. *J Heart Lung Transplant* 2007;26:466-471.
 342. Fagioli S, Cooper DK, Zuhdi N. Hepatitis C status of heart transplant recipients. *Clin Transplant* 1998;12:5-10.
 343. Doucette KE, Weinkauff J, Sumner S, Ens K, Lien D. Treatment of hepatitis C in potential lung transplant candidates. *Transplantation* 2007;83:1652-1655.
 344. Ghobrial RM, Steadman R, Gornbein J, Lassman C, Holt CD, Chen P, et al. A 10-year experience of liver transplantation for hepatitis C: analysis of factors determining outcome in over 500 patients. *Ann Surg* 2001;234:384-393; discussion 393-394.
 345. Neumann UP, Berg T, Bahra M, Puhl G, Guckelberger O, Langrehr JM, et al. Long-term outcome of liver transplants for chronic hepatitis C: a 10-year follow-up. *Transplantation* 2004;77:226-231.
 346. Neumann UP, Berg T, Bahra M, Seehofer D, Langrehr JM, Neuhaus R, et al. Fibrosis progression after liver transplantation in patients with recurrent hepatitis C. *J Hepatol* 2004;41:830-836.
 347. Yilmaz N, Shiffman ML, Stravitz RT, Sterling RK, Luketic VA, Sanyal AJ, et al. A prospective evaluation of fibrosis progression in patients with

- recurrent hepatitis C virus following liver transplantation. *Liver Transpl* 2007;13:975-983.
348. Rowe IA, Webb K, Gunson BK, Mehta N, Haque S, Neuberger J. The impact of disease recurrence on graft survival following liver transplantation: a single centre experience. *Transpl Int* 2008;21:459-465.
 349. Sheiner PA, Boros P, Klion FM, Thung SN, Schluger LK, Lau JY, et al. The efficacy of prophylactic interferon alfa-2b in preventing recurrent hepatitis C after liver transplantation. *HEPATOLOGY* 1998;28:831-838.
 350. Singh N, Gayowski T, Wannstedt CF, Shakil AO, Wagener MM, Fung JJ, et al. Interferon-alpha for prophylaxis of recurrent viral hepatitis C in liver transplant recipients: a prospective, randomized, controlled trial. *Transplantation* 1998;65:82-86.
 351. Chalasani N, Manzarbeitia C, Ferenci P, Vogel W, Fontana RJ, Voigt M, et al. Peginterferon alfa-2a for hepatitis C after liver transplantation: two randomized, controlled trials. *HEPATOLOGY* 2005;41:289-298.
 352. Mazzaferro V, Tagger A, Schiavo M, Regalia E, Pulvirenti A, Ribero ML, et al. Prevention of recurrent hepatitis C after liver transplantation with early interferon and ribavirin treatment. *Transplant Proc* 2001;33:1355-1357.
 353. Sugawara Y, Makuuchi M, Matsui Y, Kishi Y, Akamatsu N, Kaneko J, et al. Preemptive therapy for hepatitis C virus after living-donor liver transplantation. *Transplantation* 2004;78:1308-1311.
 354. Gane EJ, Lo SK, Riordan SM, Portmann BC, Lau JY, Naoumov NV, et al. A randomized study comparing ribavirin and interferon alfa monotherapy for hepatitis C recurrence after liver transplantation. *HEPATOLOGY* 1998;27:1403-1407.
 355. Firpi RJ, Abdelmalek MF, Soldevila-Pico C, Reed A, Hemming A, Howard R, et al. Combination of interferon alfa-2b and ribavirin in liver transplant recipients with histological recurrent hepatitis C. *Liver Transpl* 2002;8:1000-1006.
 356. Samuel D, Bizollon T, Feray C, Roche B, Ahmed SN, Lemonnier C, et al. Interferon-alpha 2b plus ribavirin in patients with chronic hepatitis C after liver transplantation: a randomized study. *Gastroenterology* 2003;124:642-650.
 357. Bizollon T, Ahmed SN, Radenne S, Chevallier M, Chevallier P, Parvaz P, et al. Long term histological improvement and clearance of intrahepatic hepatitis C virus RNA following sustained response to interferon-ribavirin combination therapy in liver transplanted patients with hepatitis C virus recurrence. *Gut* 2003;52:283-287.
 358. Berenguer M, Palau A, Fernandez A, Benloch S, Aguilera V, Prieto M, et al. Efficacy, predictors of response, and potential risks associated with antiviral therapy in liver transplant recipients with recurrent hepatitis C. *Liver Transpl* 2006;12:1067-1076.
 359. Berenguer M, Prieto M, Palau A, Carrasco D, Rayon JM, Calvo F, et al. Recurrent hepatitis C genotype 1b following liver transplantation: treatment with combination interferon-ribavirin therapy. *Eur J Gastroenterol Hepatol* 2004;16:1207-1212.
 360. Mukherjee S, Lyden E, McCashland TM, Schafer DF. Interferon alpha 2b and ribavirin for the treatment of recurrent hepatitis C after liver transplantation: cohort study of 38 patients. *J Gastroenterol Hepatol* 2005;20:198-203.
 361. Mukherjee S. Pegylated interferon alfa-2a and ribavirin for recurrent hepatitis C after liver transplantation. *Transplant Proc* 2005;37:4403-4405.
 362. Dumortier J, Scoazec JY, Chevallier P, Boillot O. Treatment of recurrent hepatitis C after liver transplantation: a pilot study of peginterferon alfa-2b and ribavirin combination. *J Hepatol* 2004;40:669-674.
 363. Castells L, Vargas V, Allende H, Bilbao I, Luis Lazaro J, Margarit C, et al. Combined treatment with pegylated interferon (alpha-2b) and ribavirin in the acute phase of hepatitis C virus recurrence after liver transplantation. *J Hepatol* 2005;43:53-59.
 364. Neumann U, Puhl G, Bahra M, Berg T, Langrehr JM, Neuhaus R, et al. Treatment of patients with recurrent hepatitis C after liver transplantation with peginterferon alfa-2B plus ribavirin. *Transplantation* 2006;82:43-7.
 365. Oton E, Barcena R, Moreno-Planas JM, Cuervas-Mons V, Moreno-Zamora A, Barrios C, et al. Hepatitis C recurrence after liver transplantation: Viral and histologic response to full-dose PEG-interferon and ribavirin. *Am J Transplant* 2006;6:2348-1255.
 366. Sharma P, Marrero JA, Fontana RJ, Greenon JK, Conjeevaram H, Su GL, et al. Sustained virologic response to therapy of recurrent hepatitis C after liver transplantation is related to early virologic response and dose adherence. *Liver Transpl* 2007;13:1100-1108.
 367. Samuel D, Forns X, Berenguer M, Trautwein C, Burroughs A, Rizzetto M, et al. Report of the monothematic EASL conference on liver transplantation for viral hepatitis (Paris, France, January 12-14, 2006). *J Hepatol* 2006;45:127-143.
 368. Angelico M, Petrolati A, Lionetti R, Lenci I, Burra P, Donato MF, et al. A randomized study on Peg-interferon alfa-2a with or without ribavirin in liver transplant recipients with recurrent hepatitis C. *J Hepatol* 2007;46:1009-1017.
 369. Carrion JA, Navasa M, Garcia-Retortillo M, Garcia-Pagan JC, Crespo G, Bruguera M, et al. Efficacy of antiviral therapy on hepatitis C recurrence after liver transplantation: a randomized controlled study. *Gastroenterology* 2007;132:1746-1756.
 370. Firpi RJ, Zhu H, Morelli G, Abdelmalek MF, Soldevila-Pico C, Machicao VI, et al. Cyclosporine suppresses hepatitis C virus in vitro and increases the chance of a sustained virologic response after liver transplantation. *Liver Transpl* 2006;12:51-57.
 371. Stravitz RT, Shiffman ML, Sanyal AJ, Luketic VA, Sterling RK, Heuman DM, et al. Effects of interferon treatment on liver histology and allograft rejection in patients with recurrent hepatitis C following liver transplantation. *Liver Transpl* 2004;10:850-858.
 372. Saab S, Kalmaz D, Gajjar NA, Hiatt J, Durazo F, Han S, et al. Outcomes of acute rejection after interferon therapy in liver transplant recipients. *Liver Transpl* 2004;10:859-867.
 373. Biselli M, Andreone P, Gramenzi A, Lorenzini S, Loggi E, Bonvicini F, et al. Pegylated interferon plus ribavirin for recurrent Hepatitis C infection after liver transplantation in naive and non-responder patients on a stable immunosuppressive regimen. *Dig Liver Dis* 2006;38:27-32.
 374. Oton E, Barcena R, Garcia-Garzon S, Moreno-Zamora A, Moreno A, Garcia-Gonzalez M, et al. Pegylated interferon and ribavirin for the recurrence of chronic hepatitis C genotype 1 in transplant patients. *Transplant Proc* 2005;37:3963-3964.
 375. Berenguer M, Prieto M, Rayon JM, Mora J, Pastor M, Ortiz V, et al. Natural history of clinically compensated hepatitis C virus-related graft cirrhosis after liver transplantation. *HEPATOLOGY* 2000;32:852-858.
 376. Bahra M, Neumann UP, Jacob D, Berg T, Neuhaus R, Langrehr JM, et al. Outcome after liver re-transplantation in patients with recurrent chronic hepatitis C. *Transpl Int* 2007;20:771-778.
 377. Rosen HR, Martin P. Hepatitis C infection in patients undergoing liver retransplantation. *Transplantation* 1998;66:1612-1616.
 378. Vogel W, Graziadei I, Umlauf F, Datz C, Hackl F, Allinger S, et al. High-dose interferon-alpha2b treatment prevents chronicity in acute hepatitis C: a pilot study. *Dig Dis Sci* 1996;41:81S-85S.
 379. Jaeckel E, Cornberg M, Wedemeyer H, Santantonio T, Mayer J, Zankel M, et al. Treatment of acute hepatitis C with interferon alfa-2b. *N Engl J Med* 2001;345:1452-1457.
 380. Licata A, Di Bona D, Schepis F, Shahied L, Craxi A, Camma C. When and how to treat acute hepatitis C? *J Hepatol* 2003;39:1056-1062.
 381. Gerlach JT, Diepolder HM, Zachoval R, Gruener NH, Jung MC, Ulsenheimer A, et al. Acute hepatitis C: high rate of both spontaneous and treatment-induced viral clearance. *Gastroenterology* 2003;125:80-88.
 382. Kamal SM, Fouly AE, Kamel RR, Hockenjos B, Al Tawil A, Khalifa KE, et al. Peginterferon alfa-2b therapy in acute hepatitis C: impact of onset of therapy on sustained virologic response. *Gastroenterology* 2006;130:632-638.
 383. Nomura H, Sou S, Tanimoto H, Nagahama T, Kimura Y, Hayashi J, et al. Short-term interferon-alfa therapy for acute hepatitis C: a randomized controlled trial. *HEPATOLOGY* 2004;39:1213-1219.
 384. De Rosa FG, Bargiacchi O, Audagnotto S, Garazzino S, Cariti G, Raiteri R, et al. Dose-dependent and genotype-independent sustained virological response of a 12 week pegylated interferon alpha-2b treatment for acute hepatitis C. *J Antimicrob Chemother* 2006;57:360-363.

385. Calleri G, Cariti G, Gaiottino F, De Rosa FG, Bargiacchi O, Audagnotto S, et al. A short course of pegylated interferon-alpha in acute HCV hepatitis. *J Viral Hepat* 2007;14:116-121.
386. Villano SA, Vlahov D, Nelson KE, Cohn S, Thomas DL. Persistence of viremia and the importance of long-term follow-up after acute hepatitis C infection. *HEPATOLOGY* 1999;29:908-914.
387. Cox AL, Netski DM, Mosbrugger T, Sherman SG, Strathdee S, Ompad D, et al. Prospective evaluation of community-acquired acute-phase hepatitis C virus infection. *Clin Infect Dis* 2005;40:951-958.
388. Hoofnagle JH. Course and outcome of hepatitis C. *HEPATOLOGY* 2002;36(Suppl):S21-S29.
389. Edlin BR, Seal KH, Lorvick J, Kral AH, Ciccarone DH, Moore LD, et al. Is it justifiable to withhold treatment for hepatitis C from illicit-drug users? *N Engl J Med* 2001;345:211-215.
390. Gossop M, Marsden J, Stewart D, Rolfe A. Patterns of improvement after methadone treatment: 1 year follow-up results from the National Treatment Outcome Research Study. *Drug Alcohol Depend* 2000;60:275-286.
391. Geber WF, Lefkowitz SS, Hung CY. Effect of morphine, hydromorphone, methadone, mescaline, trypan blue, vitamin A, sodium salicylate, and caffeine on the serum interferon level in response to viral infection. *Arch Int Pharmacodyn Ther* 1975;214:322-327.
392. Sylvestre DL. Treating hepatitis C in methadone maintenance patients: an interim analysis. *Drug Alcohol Depend* 2002;67:117-123.
393. Schaefer M, Schmidt F, Folwaczny C, Lorenz R, Martin G, Schindlbeck N, et al. Adherence and mental side effects during hepatitis C treatment with interferon alfa and ribavirin in psychiatric risk groups. *HEPATOLOGY* 2003;37:443-451.
394. Mehta SH, Cox A, Hoover DR, Wang XH, Mao Q, Ray S, et al. Protection against persistence of hepatitis C. *Lancet* 2002;359:1478-1483.
395. Farci P, Alter HJ, Govindarajan S, Wong DC, Engle R, Lesniewski RR, et al. Lack of protective immunity against reinfection with hepatitis C virus. *Science* 1992;258:135-140.
396. Backmund M, Meyer K, Edlin BR. Infrequent reinfection after successful treatment for hepatitis C virus infection in injection drug users. *Clin Infect Dis* 2004;39:1540-1543.
397. Golub ET, Latka M, Hagan H, Havens JR, Hudson SM, Kapadia F, et al. Screening for depressive symptoms among HCV-infected injection drug users: examination of the utility of the CES-D and the Beck Depression Inventory. *J Urban Health* 2004;81:278-290.
398. Backmund M, Meyer K, Von Zielonka M, Eichenlaub D. Treatment of hepatitis C infection in injection drug users. *HEPATOLOGY* 2001;34:188-193.
399. Matthews G, Kronborg JJ, Dore GJ. Treatment for hepatitis C virus infection among current injection drug users in Australia. *Clin Infect Dis* 2005;40(Suppl 5):S325-S329.
400. Stein MD, Maksad J, Clarke J. Hepatitis C disease among injection drug users: knowledge, perceived risk and willingness to receive treatment. *Drug Alcohol Depend* 2001;61:211-215.
401. Sylvestre DL, Litwin AH, Clements BJ, Gourevitch MN. The impact of barriers to hepatitis C virus treatment in recovering heroin users maintained on methadone. *J Subst Abuse Treat* 2005;29:159-165.
402. Renault PF, Hoofnagle JH, Park Y, Mullen KD, Peters M, Jones DB, et al. Psychiatric complications of long-term interferon alfa therapy. *Arch Intern Med* 1987;147:1577-1580.
403. Schaefer M, Hinzpeter A, Mohmand A, Janssen G, Pich M, Schwaiger M, et al. Hepatitis C treatment in "difficult-to-treat" psychiatric patients with pegylated interferon-alpha and ribavirin: response and psychiatric side effects. *HEPATOLOGY* 2007;46:991-998.
404. Wiley TE, McCarthy M, Breidi L, McCarthy M, Layden TJ. Impact of alcohol on the histological and clinical progression of hepatitis C infection. *HEPATOLOGY* 1998;28:805-809.
405. Corrao G, Arico S. Independent and combined action of hepatitis C virus infection and alcohol consumption on the risk of symptomatic liver cirrhosis. *HEPATOLOGY* 1998;27:914-919.
406. Bellentani S, Pozzato G, Saccoccio G, Crovatto M, Croce LS, Mazzoran L, et al. Clinical course and risk factors of hepatitis C virus related liver disease in the general population: report from the Dionysos study. *Gut* 1999;44:874-880.
407. Noda K, Yoshihara H, Suzuki K, Yamada Y, Kasahara A, Hayashi N, et al. Progression of type C chronic hepatitis to liver cirrhosis and hepatocellular carcinoma—its relationship to alcohol drinking and the age of transfusion. *Alcohol Clin Exp Res* 1996;20:95A-100A.
408. Pessione F, Degos F, Marcellin P, Duchatelle V, Njapoum C, Martinot-Peignoux M, et al. Effect of alcohol consumption on serum hepatitis C virus RNA and histological lesions in chronic hepatitis C. *HEPATOLOGY* 1998;27:1717-1722.
409. Romero-Gomez M, Grande L, Nogales MC, Fernandez M, Chavez M, Castro M. Intrahepatic hepatitis C virus replication is increased in patients with regular alcohol consumption. *Dig Liver Dis* 2001;33:698-702.
410. Westin J, Lagging LM, Spak F, Aires N, Svensson E, Lindh M, et al. Moderate alcohol intake increases fibrosis progression in untreated patients with hepatitis C virus infection. *J Viral Hepat* 2002;9:235-2341.
411. Hourigan LF, Macdonald GA, Purdie D, Whitehall VH, Shorthouse C, Clouston A, et al. Fibrosis in chronic hepatitis C correlates significantly with body mass index and steatosis. *HEPATOLOGY* 1999;29:1215-1219.
412. Ortiz V, Berenguer M, Rayon JM, Carrasco D, Berenguer J. Contribution of obesity to hepatitis C-related fibrosis progression. *Am J Gastroenterol* 2002;97:2408-2414.
413. Vento S, Garofano T, Renzini C, Cainelli F, Casali F, Ghironzi G, et al. Fulminant hepatitis associated with hepatitis A virus superinfection in patients with chronic hepatitis C. *N Engl J Med* 1998;338:286-290.
414. Prevention of hepatitis A through active or passive immunization: Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep* 1999;48:1-37.
415. Tsai JF, Jeng JE, Ho MS, Chang WY, Lin ZY, Tsai JH. Independent and additive effect modification of hepatitis C and B viruses infection on the development of chronic hepatitis. *J Hepatol* 1996;24:271-276.
416. Seeff LB, Lindsay KL, Bacon BR, Kresina TF, Hoofnagle JH. Complementary and alternative medicine in chronic liver disease. *HEPATOLOGY* 2001;34:595-603.
417. Strader DB, Bacon BR, Lindsay KL, La Brecque DR, Morgan T, Wright EC, et al. Use of complementary and alternative medicine in patients with liver disease. *Am J Gastroenterol* 2002;97:2391-2397.
418. Seeff LB, Curto TM, Szabo G, Everson GT, Bonkovsky HL, Dienstag JL, et al. Herbal product use by persons enrolled in the hepatitis C Antiviral Long-Term Treatment Against Cirrhosis (HALT-C) Trial. *HEPATOLOGY* 2008;47:605-612.
419. Seeff LB. Herbal hepatotoxicity. *Clin Liver Dis* 2007;11:577-596, vii.