Screening for Hepatitis C Virus Infection: A Review of the Evidence for the U.S. Preventive Services Task Force

Roger Chou, MD; Elizabeth C. Clark, MD, MPH; Mark Helfand, MD, MPH

Hepatitis C virus (HCV), the most common chronic blood-borne pathogen in the United States, is acquired primarily by large or repeated percutaneous exposures to blood.[1] In the United States, approximately 2.3% of adults 20 years of age or older are positive for anti-HCV-antibody. Between 55% to 84% of these have chronic infection,[1–6] but only 5% to 50% of infected adults are thought to know their status.[7–9]

In the United States, HCV is associated with approximately 40% of cases of chronic liver disease and 8,000 to 10,000 deaths each year.[1] Chronic HCV infection can also cause fatigue and decreased quality of life in the absence of cirrhosis or other complications.[5,10,11]

The natural course of chronic HCV infection varies. Some patients never develop histologic evidence of liver disease even after decades of infection.[12,13] In a meta-analysis of community-based cohort studies, 7% of patients with chronic HCV infection developed cirrhosis after 20 years.[14] Factors that may be associated with a more progressive course include older age at acquisition;[14,15] comorbid medical conditions, such as heavy alcohol use,[14,16–21] HIV infection,[22–24] and other chronic liver disease;[25–27] male gender;[14] and longer duration of infection. Mode of acquisition, viral load, aminotransferase levels, and viral genotype have not been consistently established as predictors of disease progression.[28–31] The effects of ethnicity on the course of HCV infection have not been well studied in the United States.[32]

In this systematic review, commissioned by the U.S. Preventive Services Task Force (USPSTF), we focus on whether it is useful to test for anti-HCV antibodies in asymptomatic adults who have no history of liver disease.

Methods

The analytic framework, definitions used, key questions, literature search, and data extraction methods are described in detail in the Appendix (available at www.annals.org). Briefly, relevant studies were identified from searches of

From the Oregon Evidence-based Practice Center (Chou, Helfand), Portland, Oregon; the Division of General Internal Medicine, and the Department of Medical Informatics and Clinical Epidemiology, Oregon Health & Science University (Chou, Helfand), Portland Oregon; University of Iowa College of Medicine (Clark), Iowa City, Iowa; and the Veterans Affairs Medical Center (Helfand), Portland, Oregon.

This study was conducted by the Oregon Evidence-based Practice Center under contract to the Agency for Healthcare Research and Quality, Contract #290-97-0018, Task Order Number 2 for the U.S. Preventive Services Task Force.

Address correspondence to Roger Chou, MD, 3181 SW Sam Jackson Park Road, Mail Code BICC, Portland, OR 97239. Phone: 503-494-5367. Pager: 503-494-9000. Fax: 503-494-4551. E-mail: chour@ohsu.edu.

Reprints are available from the AHRQ Web site (www.preventiveservices.ahrq.gov) or through the National Guideline Clearinghouse™ (www.guideline.gov). Print copies of this article, along with other USPSTF evidence summaries and Recommendations and Rationale statements, are available by subscription to the *Guide to Clinical Preventive Services, Third Edition: Periodic Updates.* The cost of this subscription is $60 and is available through the AHRQ Publications Clearinghouse (call 1-800-358-9295 or e-mail ahrqpubs@ahrq.gov).

This first appeared in *Ann Intern Med.* 2004;140:465–479.

MEDLINE® (1989 through February 2003) and the Cochrane Clinical Trials Registry (2002, Issue 2) and from the reference list of a recent evidence report commissioned by the National Institutes of Health.[33] Reference lists of retrieved articles, periodic hand searches of relevant journals, and suggestions from experts supplemented the electronic searches.

Two readers reviewed all English-language abstracts. We selected studies that provided direct evidence on the benefits of screening and studies on risk factors for HCV infection and the performance of third-generation HCV enzyme-linked immunoassay (ELISA) alone or followed by confirmatory recombinant immunoblot assay (RIBA). We focused on third-generation ELISAs because they are thought to be slightly more sensitive than second-generation tests, but included data on second-generation ELISAs from large, good-quality observational studies.[34] We also selected studies evaluating noninvasive methods to evaluate active HCV infection and the harms associated with biopsy. For treatment, we focused on trials of pegylated interferon with ribavirin but included studies that examined the effect of other interferon-based treatment regimens on long-term clinical outcomes. We also reviewed studies evaluating effects of counseling on high-risk behaviors and benefits of immunizations. Good-quality meta-analyses were reviewed when available. We excluded studies of pregnant patients; children; and patients with occupational exposures, end-stage renal disease, or HIV infection, as well as studies focusing on patients who had already developed complications of chronic HCV infection.

We used predefined criteria developed by the USPSTF, described in detail elsewhere,[35] to assess the internal validity of included studies, which we rated as "good," "fair," or "poor." We also rated the applicability of each study to the population likely to be identified by screening. We rated the overall body of evidence for each key question using the system developed by the USPSTF.[35]

This research was funded by the Agency for Healthcare Research and Quality under a contract to support the work of the U.S. Preventive Services Task Force. Agency staff and Task Force members participated in the initial design of the study and reviewed interim analyses and the final manuscript. Additional reports were distributed for review to content experts and revised accordingly.[36] Agency approval was required before this manuscript could be submitted for publication, but the authors are solely responsible for the content and the decision to submit it.

Results

Studies of Screening

We identified no randomized trials or longitudinal cohort studies comparing outcomes between patients in the general adult population who were screened and not screened for HCV infection.

Risk Factor Assessment

The identification of risk factors for the presence of HCV infection could aid in the development of selective screening strategies.[8] We identified 4 large population-based studies from the United States and Europe that evaluated rates of HCV infection and risk factors associated with HCV status.[2,3,37,38] Among these, the National Health and Nutrition Examination Survey III (NHANES III), a good-quality nationwide sample of U.S. households that was conducted from 1988 to 1994 and had 21,241 participants, found that the prevalence of positivity for anti-HCV antibodies was 1.8% overall, and 2.3% in adults older than 20 years of age.[3] Although NHANES III provides the most reliable estimate of prevalence of HCV infection in U.S. households, it probably underestimates the overall prevalence of disease because it excluded persons without addresses, institutionalized persons, and those in military service.

Independent risk factors for HCV infection found in the 4 large population-based studies are shown in Table 1.[2,3,37,38] Intravenous drug use was the strongest independent risk factor (adjusted odds ratios, 18.4–29.2) in 3 of these studies. The fourth study, NHANES III, did not assess for intravenous drug use. However, it found that cocaine and marijuana use were associated with HCV infection, perhaps because they are surrogate markers for intravenous drug use (Table 1).[3] Many other

Table 1. Data from Large Observational Studies on Independent Risk Factors for Positive Status on Tests for Anti-Hepatitis C Virus Antibody

Study (Reference) Setting	Sample Size (Prevalence of Anti-HCV Antibodies)	Risk Factors Evaluated	Adjusted Odds Ratio for Independent Risk Factors for Positive HCV-Antibody Status (95% CI)
Alter et al. National Health and Nutrition Examination Survey III[3] Population-based household sample in the United States	21 241 (1.80% overall and 2.3% in adults ≥ 20 years)	• Race or ethnicity • Sex • Marital status • Poverty index • Education • Urban residence • Region of residence • Military service status • Country of birth • Healthcare worker • Cocaine use • Marijuana use • Age at first sexual intercourse • Number of lifetime sexual partners • Herpes simplex 2 virus infection	Marital status: Divorced or separated: 1.70 (1.08–2.66) Never married, married or widowed: 1.00 Education: ≤12 years: 1.92 (1.01–3.67) >12 years: 1.00 Poverty index: Below poverty level: 2.99 (1.69–5.27) At or above poverty level: 1.00 Marijuana use: ≥100 times: 2.99 (1.69–5.27) 1–99 times: 1.15 (0.61–2.16) Never: 1.00 Cocaine use: Ever: 4.70 (2.49–8.87) Never: 1.00 Number of sexual partners: >50: 5.16 (1.80–14.73) 2–49: 2.54 (1.14–5.66) 0–1: 1.00 Age at first sexual intercourse: <18 y: 2.94 (1.50–5.78) ≥18 y: 1.00

continue

HCV = hepatitis C virus

Table 1. Data from Large Observational Studies on Independent Risk Factors for Positive Status on Tests for Anti-Hepatitis C Virus Antibody (cont)

Study (Reference) Setting	Sample Size (Prevalence of Anti-HCV Antibodies)	Risk Factors Evaluated	Adjusted Odds Ratio for Independent Risk Factors for Positive HCV-Antibody Status (95% CI)
Kaur et al. National Hepatitis Screening Survey[38] Screening program at 40 mostly urban centers in the United States	13, 997 (7.00%)	• Age • Sex • Ethnicity • Occupation • Blood transfusion • Hemodialysis • Surgery • Intravenous drug use • Sex with intravenous drug user • Sex with multiple partners • Needle-stick injury • Born in Southeast Asia or Africa • Vaccinated for hepatitis B virus infection	Sex: Male: 3.60 (2.66–4.87) Female: 1.00 Ethnicity: White or Hispanic: 0.57 (0.39–0.83) Other: 1.00 Blood transfusion: Yes: 4.09 (2.97–5.62) No: 1.00 Hemodialysis: Yes: 10.95 (3.85–31.13) No: 1.00 Intravenous drug use: Yes: 23.34 (15.21–35.81) No: 1.00 Sex with intravenous drug user: Yes: 7.29 (4.74–11.21) No: 1.00 Vaccinated for hepatitis B virus infection: Yes: 0.37 (0.22–0.62) No: 1.00
Bellentani et al. Dionysos Study[37] Population-based study in Northern Italy	6 917 (3.2%)	• Male sex • Alcohol intake >30 g/day • Hepatitis among the cohabiting • Surgical procedure • Dental procedures • Intravenous drug use • Acupuncture • Blood transfusion • Animal bites • Homosexuality	Hepatitis among cohabiting persons: Yes: 2.0 (1.4–2.8) No: 1.00 Intravenous drug use: Yes: 18.4 (5.3–64.0) No: 1.00 Animal bites: Yes: 1.6 (1.0–2.5) No: 1.00 Blood transfusion Yes: 2.2 (1.4–3.4) No: 1.00

Table 1. Data from Large Observational Studies on Independent Risk Factors for Positive Status on Tests for Anti-Hepatitis C Virus Antibody (cont)

Study (Reference) Setting	Sample Size (Prevalence of Anti-HCV Antibodies)	Risk Factors Evaluated	Adjusted Odds Ratio for Independent Risk Factors for Positive HCV-Antibody Status (95% CI)
Dubois et al.[2] Population-based study throughout France	6 283 (1.2%)	• Past or present intravenous drug abuse • Unemployment • Tattoos • History of transfusions • Travel in developing countries • Voluntary abortion • Sexually transmitted disease • Casual sex partners • Sexual contact with intravenous drug users • Surgery with major blood loss • Acupuncture • Injection with reusable glass syringe • Dental surgery • Sexual contact with • HCV-positive partner • Homosexual practices • Education level	Intravenous drug use: Yes: 29.2 (3.8–225.7) No: 1.00 History of transfusion: Yes: 7.0 (1.7–15.1) No: 1.00 Unemployment: Yes: 3.1 (1.2–8.1) No: 1.00

smaller cross-sectional studies in a variety of specific populations support the strong association between HCV infection and intravenous drug use.[39–51] Cross-sectional studies in intravenous drug users have reported prevalence rates ranging from 50% to more than 90%.[52–56]

All 4 large population-based studies also found an independent association between HCV infection and high-risk sexual behaviors (variably defined, but usually considered sex with multiple partners or sex with an HCV-infected person). In most settings with a low prevalence of intravenous drug use, high-risk sexual behaviors are the strongest risk factor for HCV infection.[56–60] It is not clear whether this association is due to a high rate of sexual transmission in specific situations[61–66] or because high-risk sexual behaviors are a marker for unacknowledged drug use.

Since 1992, transfusions have not been an important mode of HCV transmission.[56,67,68] There is insufficient evidence to determine the importance of tattoos, body piercings, shared razors, and acupuncture as risk factors.[2,67,69–75] Non-percutaneous risk factors such as gender, ethnicity, and socioeconomic status have inconsistent or weak associations with the prevalence of HCV infection.[3,38,76]

In large U.S. cross-sectional studies, between 33% and 81% of patients with HCV infection reported intravenous drug use.[38–40,77] Other retrospective studies have found that 53% to 88% of infected patients had identifiable risk factors.[78,79] Sample differences, varying stringency of risk factor ascertainment, or variation in the risk factors examined could explain some of the discrepancies between studies.[79] No study has prospectively

applied a selective screening strategy and determined how many patients were correctly identified by it.

Accuracy of HCV Antibody Testing

The terminology and interpretation of tests used to diagnose HCV infection are reviewed in the Appendix.

A recent fair-quality systematic review of third-generation ELISA (7 studies) and RIBA (3 studies) found that only 10 of 150 studies used appropriate methods for evaluating a diagnostic test.[80] We applied the USPSTF quality criteria to 9 of these 10 studies and found that all 9 had at least 1 important flaw: inclusion of a narrow patient spectrum, failure to perform a reference standard test in all samples, or lack of clarity about whether the reference standard test was interpreted independently of the screening test.[81–86] The tenth study, a study of RIBA in 51 patients receiving hemodialysis, was not referenced in the systematic review and we could not find it.

Of 7 studies that evaluated the sensitivity of third-generation ELISA and involved 4,674 patients, sensitivity ranged from 97.2% to 100% compared with the results of polymerease chain reaction (PCR) (a reference standard for active infection) or RIBA (a reference standard for exposure). We identified 3 additional studies of the sensitivity of third-generation ELISA using PCR as the reference standard (Table 2).[87–89] One of these was a good-quality study that found a sensitivity of 94% (107 of 114).[87] The specificity was 97% (946 of 976) and the positive predictive value (prevalence 10%) was 78% (107 of 137). Second-generation ELISAs are thought to be slightly less sensitive than third-generation tests, but may be more specific.[34] In data collected by the Centers for Disease Control and Prevention in 24,012 lower-prevalence (2%) patients, the positive predictive value of current second- and third-generation ELISAs without confirmatory RIBA was 42% using PCR as the reference standard.[90]

To minimize false-positive results in low-prevalence populations, positive ELISA tests are usually followed by confirmatory RIBA tests.[90] Patients with positive results on both tests are considered to have confirmed evidence of HCV exposure, although they may not have active infection. In 4 large population-based studies (prevalence 1.2% to 3.2%), the proportion of patients with positive results on ELISA confirmed by RIBA who were found to have viremia was 73% to 86% using second- or third-generation ELISAs.[2,3,37,91]

Harms from HCV Antibody Testing

False-positive screening tests could result in harms that are difficult to measure (for example, labeling, anxiety, detrimental effects on close relationships). There are few data regarding harms in patients who have false-positive tests or HCV-positive patients who do not receive treatment, though 1 fair-quality observational study suggests worse quality of life in patients who are aware of their status.[92] We found no studies investigating whether harms associated with learning HCV status could be reduced by effective patient education and counseling. However, data from 1 small trial in 34 patients found that a counseling program improved sense of well-being in women with HCV.[93]

Work-up for Treatable Disease

In addition to viral load and aminotransferase testing, the National Institutes of Health currently recommends pretreatment liver biopsy.[67] Several blood tests have been proposed as noninvasive methods of predicting biopsy findings, but in a recent good-quality systematic review, no blood test predicted liver biopsy findings accurately, particularly for intermediate stages of fibrosis.[94]

Proportion of Patients Qualifying for Treatment

In clinical practice, the number of referred patients who receive antiviral treatment depends on the degree of liver damage, the presence of serious comorbid conditions, and patient preferences regarding treatment. Antiviral therapy is recommended for patients with chronic HCV infection who are at the greatest risk for progression

Table 2. Additional Studies on the Diagnostic Accuracy of Third-Generation Enzyme-Linked Immunosorbent Assays for Anti-Hepatitis C Virus Antibodies

Study, Year (Reference)	Patients Studied	Reference Assay	Prevalence of Positive Results on Anti-HCV ELISA	Sensitivity	Specificity	Positive Predictive Value	Quality Rating
Huber et al., 1996[87]	Patients admitted because of acute liver disease or suspected chronic hepatitis	PCR	10% (107/1090)	94% (107/114)	97% (946/976)	78% (107/137)	Good
Prince et al., 1997[89]	Blood donors with elevated alanine aminotransferase levels	PCR	18% (54/301)	100% (51/51)	98.8% (247/250)	94% (51/54)	Fair Narrow patient spectrum
Busch et al., 2000[88]	Blood donors with positive screening test who were retested	Second-generation RIBA or PCR	100% (1091/1091)	99.2% (1082/1091)	Not calculable	Not calculable	Fair Performance of reference assays not standardized, narrow patient spectrum

ELISA = enzyme-linked immunosorbent assay; HCV = hepatitis C virus; PCR = polymerase chain reaction; RIBA = recombinant immunoblot assay.

to cirrhosis. These persons have HCV viremia, persistently elevated aminotransferase levels, or liver biopsy findings showing significant fibrosis or inflammation and necrosis.[1,67,95–98] In patients with minimal or no biopsy abnormalities, the benefits of treatment are not clear, and decisions about therapy are individualized.[67,69,98,99] Many patients identified by screening are likely to be in this category. In 3 community-based cohort studies, the rate of chronic hepatitis of minimal grade or with no inflammation was 43% to 61%.[4–6] Patients with cirrhosis or serious comorbid medical or psychiatric conditions also must have the risks and benefits of antiviral treatment carefully weighed.

We identified 3 fair-quality observational studies in referral centers (involving 100, 327, and 557 patients, respectively) that evaluated the number of patients referred for HCV infection who received treatment.[100–102] In these studies, 30% to 40% of evaluated patients received treatment. Common reasons for ineligibility were ongoing substance abuse (13% to 44%) and serious comorbid medical or psychiatric conditions (12% to 34%). Non-adherence to the protocol (37%) and declining to receive therapy (10%) were also reported in one study.[102]

Harms from Work-up for Active HCV Infection

In the work-up of patients with chronic HCV infection, percutaneous liver biopsy is associated with the highest risk for complications. The most common

complication of liver biopsy is pain; approximately 30% of patients require strong analgesic medications.[103] More serious but less common complications include bleeding (the most frequent major complication), biliary rupture, intestinal perforation, vasovagal hypotension, or infection.

Most data on risks of percutaneous liver biopsy come from large, fair-quality series of patients undergoing liver biopsy for a variety of reasons.[104–109] The study of highest quality (independent assessment, standard assessment form) evaluated consecutive percutaneous liver biopsies in a nationwide sample in the United Kingdom.[107] A bleeding rate of 26 of 1,500 (1.7%) was found, with 11 of 1,500 (0.7%) requiring transfusion. Death was definitely associated with biopsy in 2 of 1,500 patients and was possibly associated with biopsy in another 3, yielding a mortality rate of 0.13% to 0.33%. Because a substantial proportion of patients in this study had malignant disease, patients with chronic HCV infection may have been overestimated.[109] The rates of major complications in other large series were 0% to 3.7% (mortality rates typically <0.1%).[104,106,110] In large series, the material obtained was inadequate for diagnosis in 1.5% to 5% of cases.[107,108]

Two small studies involving 126 and 166 patients, respectively, reported complication rates from percutaneous biopsy in patients specifically with HCV infection.[111,112] In both studies, which included patients with known or suspected cirrhosis, no major complications were reported.

Small studies suggest that ultrasound-guided biopsies may be associated with fewer complications than blind biopsies.[110,112–115] Increased experience of the person performing the liver biopsy has also been associated with fewer complications.[105,107,108]

Antiviral Treatment Efficacy for Intermediate Outcomes

Because of the large number of patients and long duration required to demonstrate improvements in long-term clinical outcomes, intermediate outcomes have been the most common measure of treatment benefit. Sustained virologic response rates (absence of viremia 6 months after completion of a treatment course) are currently considered the best indication of successful treatment.[116]

Antiviral treatment began in 1986 with the use of interferon-alpha.[117] Meta-analyses of interferon trials report sustained virologic response rates of 6% to 21% for interferon monotherapy, compared to about 2% in untreated controls.[118–121] Combination interferon plus ribavirin was approved in 1998 and was found in 3 good-quality systematic reviews to be superior (sustained virologic response, 33% to 41%) to interferon monotherapy.[119–121] Treatment with pegylated interferon, alone or in combination with ribavirin, has been used for only a few years. For all interferon-based regimens, factors associated with successful treatment include genotypes other than 1, lower baseline viral load, less serious biopsy findings, and less body surface area or lower weight.[67]

We reviewed 3 randomized controlled trials of pegylated interferon plus ribavirin versus pegylated interferon alone for 24 to 48 weeks (Table 3). Two trials[122,123] were large, multi-center, good-quality randomized controlled trials involving 1,121 and 1,530 patients, and the other was a small, fair-quality study involving 72 patients.[124]

The 2 good-quality trials found that 54% to 56% of all patients achieved a sustained virologic response with pegylated interferon plus ribavirin versus 44% to 47% with pegylated interferon monotherapy ($P \leq 0.01$).[122,123] One of these trials also found a higher sustained virologic response rate with pegylated interferon plus ribavirin compared with non-pegylated interferon plus ribavirin (56% vs. 44%; $P<0.001$).[122] Table 4 summarizes the relative effects of each interferon-based regimen, with estimated numbers needed to treat for benefit.

Treatment studies may not be directly applicable to the population that would be identified by screening because they evaluate patients who probably have more serious disease. In addition, a significant proportion of patients identified by screening would not meet inclusion criteria used by antiviral trials. For example, 6[122,123,125–128] out of 7[124] trials of pegylated interferon used elevated aminotransferase levels as an inclusion criterion. In large, population-based studies, 46% to 67% of patients with viremia had normal aminotransferase levels.[2,37,91]

Table 3. Randomized Controlled Trials of Pegylated Interferon plus Ribavirin in Patients with Hepatitis C Virus Infection

Study, Year (Reference)	Patients Enrolled/ Analyzed	Interventions	Sustained Viral Response 6 Months after Treatment	Adverse Events	Internal Validity Rating	Relevance to Screening
Fried 2002[122]	1149/1121	a. INF alfa-2b, 3 MU 3 times per wk + ribavirin 1000–1200 mg/d	44%	For a vs. b vs. c Dose reduction: not clear Discontinuation (%): 32 vs. 32 vs. 22 Fatigue (%): 55 vs. 44 vs. 54 Headache (%): 52 vs. 51 vs. 47 Fever (%): 56 vs. 38 vs. 43 Myalgia (%): 50 vs. 42 vs. 42 Nausea (%): 33 vs. 26 vs. 29 Depression (%): 30 vs. 20 vs. 22 Dermatitis (%): 22 vs. 11 vs. 21 Deaths: 3, none thought to be related to treatment	Good	Fair: required liver biopsy findings consistent with chronic hepatitis and elevated ALT level within the past 6 months
		b. PEG INF alfa-2a, 180 ug/kg of body weight once weekly	29%			
		c. PEG INF alfa-2a 180 ug/kg once weekly + ribavirin 1000–1200 mg/d	56%† (a vs c, b vs c $P<0.001$)			

continue

† $P < 0.001$ for 1 vs. 3, 2 vs. 3.

‡ $P = 0.01$ for 1 vs. 3.

ALT = alanine aminotransferase; HCV = hepatitis C virus; INF = interferon; NR = not reported; PCR = polymerase chain reaction.

Table 3. Randomized Controlled Trials of Pegylated Interferon plus Ribavirin in Patients with Hepatitis C Virus Infection (cont)

Study, Year (Reference)	Patients Enrolled/ Analyzed	Interventions	Sustained Viral Response 6 Months after Treatment	Adverse Events	Internal Validity Rating	Relevance to Screening
Manns 2001[123]	1530/1530	a. INF alfa 2b, 1.5 ug/kg 3 times/wk + ribavirin 1000–1200 mg/d	47%	For a vs. b vs. c Dose reduction (%): 34 vs. 36 vs. 42 Discontinuation (%): 13 vs. 13 vs. 14 Fatigue (%): 60 vs. 62 vs. 64 Headache %): 58 vs. 58 vs. 62 Myalgia (%): 50 vs. 48 vs. 56 Fever (%): 33 vs. 44 vs. 46 Diarrhea (%): 17 vs. 16 vs. 22 Depression (%): 34 vs. 29 vs. 31 Injection site reaction (%): 36 vs. 59 vs. 58 Deaths: 0	Good	Fair: required liver biopsy findings consistent with chronic hepatitis and elevated ALT levels
		b. Pegylated INF alfa 2b, 1.5 ug/kg once weekly for 4 wk then 0.5 ug/kg for 44 wk + ribavirin 1000–1200 mg/d for 48 wk	47%			
		c. PEG INF alfa 2b, 1.5 ug/kg once weekly + ribavirin 800 mg/d for 48 wk	54%‡ (a vs. c *P*=0.01)			

Table 3. Randomized Controlled Trials of Pegylated Interferon plus Ribavirin in Patients with Hepatitis C Virus Infection (cont)

Study, Year (Reference)	Patients Enrolled/ Analyzed	Interventions	Sustained Viral Response 6 Months after Treatment	Adverse Events	Internal Validity Rating	Relevance to Screening
Glue 2000[124]	72/72	a. Pegylated INF alfa 2b, 0.35 ug/kg once weekly	0%	*Dose reduction: NR* *Dose discontinued: 1 patient (treatment group not specified)* *Influenza symptoms (%): 17–44* *Headache (%): 50–56* *Asthenia (%): 0–22* *Mean reduction in hemoglobin level: 1.5–2.5 g/dL*	Fair Allocation concealment inadequate, not clear if groups similar at baseline, outcomes assessors not blinded	Unclear: numbers screened and eligible not reported, baseline characteristics inadequately described
		b. Pegylated INF alfa 2b, 0.70 ug/kg once weekly	44%			
		c. Pegylated INF alfa 2b, 1.40 ug/kg once weekly	42%			
		d. Pegylated INF alfa 2b, 0.35 ug/kg once weekly + ribavirin 600–800 mg/d	17%			
		e. Pegylated INF alfa 2b, 0.70 ug/kg once weekly + ribavirin 600–1200 mg/d	53%			
		f. Pegylated INF alfa 2b, 1.40 ug/kg once weekly + ribavirin 600–1200 mg/d	60%			

Table 4. Sustained Virologic Response Rates with Different Antiviral Regimens for Hepatitis C Virus Infection

Treatment	Sustained Virologic Response Rate 6 Months after Treatment	Number Needed to Treat for One Sustained Virologic Response Compared with Placebo	Source, Year (Reference)
Placebo	<2%	Not applicable	Poynard et al., 1996[118]*
Interferon monotherapy	6–16%	6–17	Poynard et al., 1996[118]* Gebo et al., 2002[33]* Kjaergard et al., 2001[119]* Shepherd et al., 2000[121]*
Interferon plus ribavirin	33–41%	2.4–3.0	Gebo, 2002[33]* Kjaergard et al., 2001[119]* Shepherd et al., 2000[121]*
Pegylated interferon alone	25–39%	2.6–4.0	Heathcote et al., 2000[125] Lindsay et al., 2001[126] Reddy et al., 2001[127] Zeuzem et al., 2000[128]
Pegylated interferon plus ribavirin	54–60%	1.6–1.8	Fried et al., 2002[122] Glue et al., 2000[124] Manns et al., 2001[123]

*Systematic review or meta-analysis.

Antiviral Treatment Efficacy for Clinical Outcomes

The long duration for important complications to develop and the relatively short time period that treatments have been available complicate our ability to assess the long-term benefits of antiviral treatment. There are no data on long-term benefits after treatment with pegylated interferon alone, pegylated interferon combined with ribavirin, or non-pegylated interferon combined with ribavirin.[119]

One recent good quality systematic review of 3 randomized controlled trials and 13 cohort studies evaluated the long-term effects (viremia or clinical outcomes) of non-pegylated interferon monotherapy.[120] The studies were heterogeneous in design, had some methodological limitations, and did not consistently show that treated patients had better long-term clinical outcomes than untreated patients.

We independently reviewed the 2 randomized controlled trials that reported long-term clinical outcomes after treatment with interferon (Table 5). In an unblinded, fair-quality Japanese trial, 90 patients were randomly assigned to interferon-alpha for 24 weeks or symptomatic treatment. After 8.7 years, rates of hepatocellular carcinoma (27% vs.

Table 5. Randomized Controlled Trials with Long-Term Clinical Outcomes in Patients with Hepatitis C Infection after Treatment with Interferon*

Study, Year (Reference)	Patients Analyzed (*n*) and Duration of Followup	Interventions	Long-Term Outcomes	Internal Validity	Applicability to Screening
Nishiguchi 2001[129]	90 Mean 8.7 y	a) INF-alfa 6 MU 3 times weekly for 24 wk b) Symptomatic treatment	a vs. b Hepatocellular carcinoma: 27% vs. 73% (P<0.001); adjusted RR 0.256 [95% CI, 0.125–0.522]) Death: 11% vs. 58% (P<0.001); adjusted RR 0.135 [95% CI, 0.049–0.372]) Adjusted RR for progression to Child B cirrhosis: 0.250 (0.124–0.505)	Fair Not blinded	Unclear Required elevated ALT and liver biopsy consistent with active cirrhosis; incidence of hepatocellular cancer and death much higher in untreated Japanese populations than in the United States
Bernardinello 1999[130]	61 Up to 5 y	a) Intramuscular INF-beta 6 MU 3 times weekly for 6 mo then 3 M 3 times weekly for 6 mo b) No treatment	a vs. b (not statistically significant) Cumulative probability of decompensation: 24% vs. 35% Risk for death: 9% vs. 4.4% Hepatocellular carcinoma: 5.3% (2 cases) vs. 4.3% (1 case)	Fair Attrition, crossovers, and contamination not reported; possibility of differential loss to followup not reported	Unclear Required elevated ALT and liver biopsy findings consistent with active cirrhosis

*Numbers in square brackets are 95% CIs.
ALT = alanine aminotransferase; INF = interferon; RR = relative risk.

73%; P<0.0001) and mortality (11% vs. 58%; P<0.001) were significantly reduced in the interferon-treated patients.[129] The relative risk for progressing to Child B cirrhosis was 0.250 (95% CI, 0.124 to 0.505) in the treatment group versus the control group. In a fair-quality Italian randomized controlled trial, no significant differences in long-term outcomes were found up to 5 years after randomization to interferon-beta or placebo (hepatocellular cancer 5.3% vs. 4.3%).[130]

The single randomized, controlled trial and many of the cohort studies showing significantly improved

long-term outcomes after interferon monotherapy were conducted in Japan, and may not be applicable to settings in the United States. Some evidence shows that chronic HCV infection in Japan is associated with substantially higher rates of serious complications.[33,129,131,132]

Quality of life has generally been evaluated by comparing results in patients who achieved a sustained viral response and those who did not. We identified only 1 randomized controlled trial that analyzed quality-of-life outcomes according to whether patients received antiviral treatment or placebo.[133] This study was rated as poor quality because results were available for only 53 of 106 patients randomly assigned to interferon, baseline quality-of-life scores appeared significantly different between groups, and it was unclear whether patients were blinded to markers of response to treatment. Patients randomly assigned to interferon had no significant change in total Sickness Impact Profile score compared with baseline.

Efficacy of Counseling and Immunizations

Counseling asymptomatic patients found to have HCV infection might help prevent spread of disease or decrease the likelihood of progressive disease.[70] Specifically, patients could be counseled to obtain immunizations for hepatitis A virus or hepatitis B virus, avoid excess alcohol, or avoid sharing needles or engaging in other risky practices.[134]

Hepatitis A and hepatitis B vaccinations in patients with HCV infection have been found to be immunogenic and safe.[135] We identified no studies evaluating the effect of vaccinations after diagnosis of HCV on subsequent clinical outcomes. Although a widely-publicized Italian study[136] reported high rates of fulminant (7 of 17) and fatal (6 of 17) hepatitis in patients with HCV infection who acquired hepatitis A infection, other studies.[137,138] have reported much lower rates. According to data from the Centers for Disease Control and Prevention, mortality rates from hepatitis A virus infection are higher in patients with underlying chronic liver disease (4.6% [107 of 2,311]) than those without it (0.2% [247 of 113,009]), but it is not clear how many of these deaths were associated with HCV infection.[135]

We identified no studies evaluating the effect of post-diagnosis counseling regarding alcohol consumption or other high-risk behaviors on subsequent clinical outcomes or spread of disease. We also did not identify any studies that estimated rates of spread of disease in patients aware of their status compared with those who were unaware. One poor-quality French observational study found less "excessive" alcohol consumption after diagnosis of HCV infection, but the results may have been affected by recall bias or patients' unwillingness to admit to current heavy alcohol use.[139] One small U.S. study found no significant differences in behaviors in young injection drug users aware of their HCV status compared with those who were unaware.[140]

Harms from Antiviral Treatment

Interferon-based treatments are commonly associated with self-limited adverse events. The most common adverse event is an influenza-like syndrome involving myalgias, fevers, and fatigue. A good-quality systematic review found that serious or life-threatening side effects occurred in 1% to 2% of patients receiving interferon monotherapy.[118] Patients with significant comorbid conditions were generally excluded from randomized controlled trials. Because of the long duration (6 months) of interferon regimens, adverse effects of treatment can have significant (although usually self-limited) effects on quality of life.

Three randomized controlled trials provided data about adverse effects associated with combination therapy with pegylated interferon plus ribavirin or pegylated interferon monotherapy (Table 3).[122–124] In all of the studies, rates of adverse events were similar in both groups (50% to 60%). No serious complications or deaths from treatment were reported. In addition to dose-related influenza-like symptoms, psychiatric, gastrointestinal, dermatologic, and mild self-limited hematologic adverse effects were also common. Withdrawal rates in the pegylated interferon plus ribavirin group in 2 good-quality studies[122,123] were 14% and 22%, compared with 13% to 32% in the nonpegylated

interferon plus ribavirin group. Two good-quality systematic reviews found withdrawal rates of 8% to 9% in trials of patients receiving non-pegylated interferon monotherapy.[119,121]

Relationship of Intermediate Outcomes to Clinical Outcomes

In 5 uncontrolled retrospective and prospective studies of patients who received antiviral treatment, complete responders (sustained virologic response and sustained biologic response) had a moderately decreased risk for hepatocellular cancer and cirrhosis compared with those who had relapses or those who did not respond.[33,120,141] However, these studies did not consistently find a decreased risk for hepatocellular cancer in nonresponders compared with untreated controls. These studies were heterogeneous in design and had some methodologic limitations. Specifically, this body of literature does not exclude the possibility that favorable, unknown underlying prognostic factors led to a better response to treatment and better long-term outcomes.

In 4 clinical trials of treatment-naïve patients with HCV infection, 3 of which were fair quality[142–144] and 1 of which was poor quality,[133] a sustained virologic response was associated with better functional status 24 weeks after treatment (Table 6).[142–144] The 3 fair-quality studies found that sustained responders had better scores than nonresponders on the 36-Item Short-Form Health Survey (SF36) in 5 to 8 of 8 domains. In all of these studies, patients could have been aware of the results of biochemical or virologic testing before SF-36 testing was repeated.

Discussion

The results of the evidence review are summarized in Table 7. No direct evidence shows benefits of screening for HCV infection in the general adult population. There are inadequate data to accurately weigh the benefits and risks of screening for HCV in the otherwise healthy, asymptomatic adults. Although screening can accurately detect chronic HCV infection and antiviral treatment can successfully eradicate viremia, there are inadequate data to estimate

Table 6. Differences in Baseline and 24-Week Scores on the 36-Item Short-Form Health Survey between Patients with Hepatitis C Virus Infection Who Had a Sustained Virologic Response Compared with Nonresponders*

SF-36 Categories	Difference in SF-36 scores†		
	Bernstein 2002[142]	Bonkovsky 1999[143]	McHutchinson 2001[144]‡
Physical function	4.6§	6‖	2.5
Ability to perform physical roles	9.8§	22¶	5
Degree of bodily pain	2.9¶	–1	1.5
Sense of general health	9.1§	7¶	5
Overall sense of vitality	9.6§	8‖	4.5
Social function	6.2§	9‖	3
Ability to perform emotional roles	8.4¶	11	3
Overall sense of mental health	4.6§	4	2.5

† Reported as difference from baseline to 24 weeks after starting treatment in responders compared with nonresponders.
†† Difference in standard deviation of change from baseline. Statistical significance was not reported. The other studies reported differences in absolute scores.
§ $P<0.001$
‖ $P<0.05$
¶ $P< 0.01$
SF-36 = 36-Item Short-Form Health Survey.

Table 7. Summary of Findings of Evidence Synthesis on Screening for Hepatitis C Infection

Key Question	Level and Type of Evidence†	Overall Evidence for the Link‡	Findings
1. Does screening for HCV reduce the risk for or rate of harm and premature death and disability?	None.	N/A	No direct evidence regarding benefits of screening in the general population.
2. Can clinical or demographic characteristics identify a subgroup of asymptomatic patients at higher risk for infection?	II-3 Cross-sectional studies	Good for persons with intravenous drug use, high-risk sexual behaviors, and transfusions prior to 1992. Fair for other risk factors.	Intravenous drug use is the most important risk factor for HCV infection. High-risk sexual behaviors are another important risk factor. Transfusions prior to 1992 remain a risk factor. Other risk factors have inconsistent associations with HCV infection. No prospective study has applied a screening strategy in the general population and measured what proportion of patients was identified correctly.
3. What are the test characteristics of HCV antibody testing?	Studies of diagnostic test characteristics.	Fair	Using viremia as the reference standard, sensitivity of third-generation ELISA testing appears to be 94% or higher. Limited data found a specificity of 97% or greater using viremia as the reference standard.
4. What is the predictive value of a positive screening test, and what are the harms associated with screening for HCV infection?	II-3. Cross-sectional studies.	Good for positive predictive values. Poor for harms.	Large population-based studies found that the positive predictive value for viremia of positive results on ELISA with confirmatory positive results on RIBA was 73%–86%. There are almost no data on the harms of screening.
5a. What are the test characteristics of the work-up for treatable disease?	One good systematic review.	Fair	Blood tests have only modest value in predicting fibrosis on liver biopsy.
5b. In patients found to be positive for HCV, what proportion of patients would qualify for antiviral treatment?	II-3. Cohort studies and cross-sectional studies.	Fair	30–40% of patients referred for treatment received treatment.

† Evidence codes are based on study design categories.[35] I = evidence obtained from at least one properly randomized, controlled trial; II-1 = evidence obtained from well-designed controlled trials without randomization; II-2 = evidence obtained from well-designed cohort or case-control analytic studies; II-3 = evidence obtained from multiple time series or dramatic uncontrolled experiments.
‡ Based on criteria developed by the U.S. Preventive Services Task Force.[35]
ELISA = enzyme-linked immunoassay; HCV = hepatitis C virus; NA = not applicable;
RIBA = recombinant immunoblot assay

Table 7. Summary of Findings of Evidence Synthesis on Screening for Hepatitis C Infection (cont)

Key Question	Level and Type of Evidence†	Overall Evidence for the Link‡	Findings
6. What are the harms associated with the work-up for active HCV disease?	II-2. Cohort studies	Fair	In the highest-quality trial, the risk of major complications (bleeding, death, perforation) from liver biopsy was approximately 1%–2%, with mortality less than 0.3%. The risks may be lower in patients undergoing liver biopsy specifically for evaluation of HCV infection.
7a. How well does antiviral treatment reduce the rate of viremia, improve aminotransferase levels, and improve histology?	I. Well-designed randomized clinical trials.	Good	Newer treatments have achieved sustained virologic response rates of 54–60%. (54–60% with pegylated interferon + ribavirin) compared with older treatments. Trials were performed in patients referred for treatment.
7b. How well does antiviral treatment improve health outcomes in asymptomatic patients with HCV infection?	I, II-2. Cohort studies and clinical trials.	Fair	Limited data, primarily from Japan, has found improved clinical outcomes in patients receiving antiviral treatment. Data on long-term quality of life outcomes is sparse.
7c. How well do counseling and immunizations improve outcomes in asymptomatic patients with HCV infection or prevent spread of disease?	II-3. Case-control and cross-sectional studies.	Poor	There is insufficient evidence to estimate the effects of counseling or immunizations on intermediate or clinical outcomes.
8. What are the harms (including intolerance to treatment) associated with antiviral intervention?	I. Well-designed randomized clinical trials.	Good	Common adverse events with interferon-based therapy are self-limited influenza-like symptoms, which occur in 50%–60%. Major complications occur in 1%–2% of patients. Withdrawals due to adverse events occurred in 14%–22% of patients on pegylated interferon plus ribavirin combination therapy.
9. Have improvement in intermediate outcomes been shown to reduce the risk or rate of harm from HCV infection?	II-2. Fair-quality cohort studies and clinical trials.	Fair	There is some evidence that intermediate outcomes are associated with improved clinical outcomes, but methodologic concerns limit interpretation of this data.

Table 8. Estimated Yield of Screening for Hepatitis C Virus in 2 Hypothetical Cohorts

Variable	Base-Case Assumptions	Source (Reference)	Adults with HCV Infection among 1000 Average-Risk Adults Screened	Adults with HCV Infection among 1000 Adults Screened Who Reported IV Drug Use
Prevalence of anti-HCV antibodies in population	2% in general U.S. population 50 to >90% in U.S. patients with past or current IVDU	NHANES III[3] (1.8% in general population, 2.3% in adults >20 years old) Numerous cross-sectional studies	20	500–900
Proportion of anti-HCV antibody positive patients (positive results on ELISA followed by confirmatory RIBA) with viremia	73%–86%	NHANES III,[3] Dionysos study (Italy),[37] French population-based study,[2] Italian population-based study[91]	15–17	365–774
Proportion of patients with viremia who will develop cirrhosis after 10–20 y	0%–10%	Systematic review of community-based cohorts of patients with HCV infection[14]	0–1.7	0–77
Proportion of patients with viremia who have abnormal aminotransferase levels	54%–66%	Dionysos study (Italy),[37] French population-based study,[2] Italian population-based study[91]	8–11	197–511
Proportion of patients undergoing liver biopsy who have major complications	1%–2% for major complications (bleeding, death, perforation) <0.3% mortality	1 large fair-quality observational study with independent ascertainment of complications in patients referred for biopsy for a variety of indications;[107] numerous other poor- and fair-quality observational studies (small studies of patients with HCV infection suggest a lower rate of complications)	0.15–0.34 major complications and <0.05 deaths if all patients with viremia undergo biopsy 0.08–0.22 major complication and <0.03 death if only patients with abnormal aminotransferase levels undergo biopsy	4–15 major complications and 0–2 deaths 2–10 major complications and 0–1.5 deaths

HCV = hepatitis C virus; IV = intravenous; NHANES III = National Health and Nutrition Examination Survey III.

Table 8. Estimated Yield of Screening for Hepatitis C Virus in 2 Hypothetical Cohorts (cont)

Variable	Base-Case Assumptions	Source (Reference)	Adults with HCV Infection among 1000 Average-Risk Adults Screened	Adults with HCV Infection among 1000 Adults Screened Who Reported IV Drug Use
Proportion of patients referred for evaluation of HCV infection who received therapy	30%	3 fair-quality observational studies of patients referred for evaluation of HCV infection[100–102]	4–5, if all patients with viremia referred	110–232
			2–3, if only patients with abnormal aminotransferase levels referred	59–153
Proportion of patients who received interferon-based therapy who completed treatment course	80%–90%	Numerous good-quality randomized trials and systematic reviews[33,118–128]	4–5, if all patients with viremia referred	88–209
			2–3, if only patients with abnormal aminotransferase levels referred	47–138
Proportion of patients who received interferon-based therapy who had a serious or life-threatening adverse event	1%–2%	Numerous good-quality randomized trials and systematic reviews[33,118–128]	0.04–0.09, in all patients with viremia referred	1–4
			0.02–0.06, if only patients with abnormal aminotransferase levels referred	0.5–2.8
Proportion of patients who receive treatment that have a sustained virologic response to best available therapy (pegylated interferon and ribavirin)	54%–60% for pegylated interferon and ribavirin combination therapy	3 randomized clinical trials (2 good-quality, 1 fair-quality) for pegylated interferon and ribavirin[122–124]	2–3, if all patients with viremia referred	59–139
			1–2, if only patients with abnormal aminotransferase levels referred	32–92

benefits of treatment for long-term clinical outcomes such as death, cirrhosis, hepatocellular cancer, and quality of life. There are also no data to estimate benefits from vaccinations or counseling about alcohol use and high-risk behaviors.

Clinical trials of antiviral treatment have been performed in referred patients, who generally have more serious and progressive disease than patients followed in community-based cohorts. Even if treatment is equally effective for virology end points in patients identified by screening and those studied in clinical trials, the overall clinical benefit would be expected to be smaller since the underlying progression rate is lower. Although the proportion of screened patients found to have chronic HCV in selected high-risk populations, particularly intravenous drug users, would be substantially higher than in the general population, there are also no data to accurately weigh the risks and benefits of selective screening. Table 8 estimates the yield from screening in hypothetical cohorts of 1,000 adults in the general population and 1,000 intravenous drug users.

Important gaps remain in our understanding of the natural history of untreated patients with HCV infection who are likely to be identified by screening. If untreated chronic HCV infection causes important morbidity in the absence of cirrhosis, there may be other important goals to be obtained from treatment, but few studies have adequately assessed the impact of treatment on quality of life or symptoms. Additional studies are needed to define the progression from asymptomatic to symptomatic HCV infection and how long symptomatic patients remain unidentified without screening.

Many studies showing improvement in long-term clinical outcomes have been conducted in Japan. Chronic HCV infection appears to follow a substantially more aggressive course in Japan than in the United States. Although lead-time bias could explain some of the observed differences in disease progression rates, the case for screening would be greatly strengthened by data showing that treatment in earlier, asymptomatic stages of disease in western countries is associated with improved outcomes compared to treatment reserved for patients who have become symptomatic and could be identified without screening. Studies demonstrating important individual or public health benefits from counseling, immunizations, and behavioral changes after a diagnosis of HCV would also greatly strengthen the case for screening. Little is known about the benefits and risks of treatment in patients typically excluded from or under-represented in randomized trials, such as those with ongoing substance abuse, those with comorbid conditions, elderly persons, and persons of non-white ethnicity).[145]

No studies have adequately assessed the potential harmful effects of screening for HCV infection, such as anxiety, labeling, or damage to close relationships, and whether these factors can be minimized by appropriate counseling. Additional studies on the long-term effects of antiviral treatment in nonresponders are important because studies have not consistently found an improved outcome in this group compared with untreated controls.

Reasonable screening strategies might be to screen adults with established risk factors, adults in settings with a high prevalence of HCV, or all adults in the general population. Studies that adequately assess the usefulness of risk factor assessment to guide selective screening strategies and the harms and benefits of selective versus universal screening are needed. A potential barrier to screening patients on the basis of risk factors is the difficulty in obtaining accurate histories of intravenous drug use or high-risk sexual behaviors. Little is known about patient preferences for screening. There are no data to estimate risks and benefits of 1-time screening versus other screening strategies.

Complications from chronic HCV present an enormous health burden that is expected to increase 2- to 4-fold over the next 2 to 4 decades. Further research to more accurately determine the benefits and harms of screening is of paramount importance.

Acknowledgments

The authors thank Susan Wingenfeld and Kathryn Pyle Krages, AMLS, MA for their administrative support, and Heidi Nelson, MD, MPH, for reviewing the manuscript.

References

1. Recommendations for prevention and control of hepatitis C virus (HCV) infection and HCV-related chronic disease. Centers for Disease Control and Prevention. *MMWR—Morbidity & Mortality Weekly Report.* 1998;47(RR-19):1–39.

2. Dubois F, Desenclos JC, Mariotte N, Goudeau A. Hepatitis C in a French population-based survey, 1994: seroprevalence, frequency of viremia, genotype distribution, and risk factors. The Collaborative Study Group. *Hepatology.* 1997;25(6):1490–1496.

3. Alter MJ, Kruszon-Moran D, Nainan OV, et al. The prevalence of hepatitis C virus infection in the United States, 1988 through 1994. *New England Journal of Medicine.* 1999;341(8):556–562.

4. 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(1):91–96.

5. Kenny-Walsh E. Clinical outcomes after hepatitis C infection from contaminated anti-D immune globulin. Irish Hepatology Research Group. *New England Journal of Medicine.* 1999;340(16):1228–1233.

6. Barrett S, Goh J, Coughlan B, et al. The natural course of hepatitis C virus infection after 22 years in a unique homogenous cohort: spontaneous viral clearance and chronic HCV infection. *Gut.* 2001;49(3):423–430.

7. Culver DH, Alter MJ, Mullan RJ, Margolis HS. Evaluation of the effectiveness of targeted lookback for HCV infection in the United States-interim results. *Transfusion.* 2000;40(10):1176–1181.

8. Singer ME, Younossi ZM. Cost effectiveness of screening for hepatitis C virus in asymptomatic, average-risk adults. *American Journal of Medicine.* 2001;111(8):614–621.

9. Gordon FD. Cost-effectiveness of screening patients for hepatitis C. *American Journal of Medicine.* 1999;107(6B):36S–40S.

10. Koff RS. Impaired health-related quality of life in chronic hepatitis C: the how, but not the why. *Hepatology.* 1999;29(1):277–279.

11. Foster GR, Goldin RD, Thomas HC. Chronic hepatitis C virus infection causes a significant reduction in quality of life in the absence of cirrhosis. *Hepatology.* 1998;27:209–212.

12. Puoti C, Castellacci R, Montagnese F. Hepatitis C virus carriers with persistently normal aminotransferase levels: healthy people or true patients? *Digestive & Liver Disease.* 2000;32(7):634–643.

13. Seeff LB. Natural history of chronic hepatitis C. *Hepatology.* 2002;36:S35–S46.

14. Freeman AJ, Dore GJ, Law MG, et al. Estimating progression to cirrhosis in chronic hepatitis C virus infection. *Hepatology.* 2001;34:809–816.

15. Poynard T, Aubert A, Lazizi Y, et al. Independent risk factors for hepatocellular carcinoma in French drinkers. *Hepatology.* 1991;13(5):896–901.

16. Harris DR, Gonin R, Alter HJ, et al. The relationship of acute transfusion-associated hepatitis to the development of cirrhosis in the presence of alcohol abuse. *Annals of Internal Medicine.* 2001;134(2):120–124.

17. Peters MG, A. TN. Alcohol use and hepatitis C. *Hepatology.* 2002;36(5 Suppl 1):S220–S225.

18. 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(3):805–809.

19. Pessione F, Degos F, Marcellin P, et al. Effect of alcohol consumption on serum hepatitis C virus RNA and histological lesions in chronic hepatitis C. *Hepatology.* 1998;27(6):1717–1722.

20. Caldwell SH, Jeffer LJ, Ditomaso A, et al. Antibody to hepatitis C is common among patients with alcohol liver disease with and without risk factors. *American Journal of Gastroenterology.* 1991;86(9):1219–1223.

21. Degos F. Hepatitis C and alcohol. *Journal of Hepatology.* 1999;31(Suppl 1):113–118.

22. Lesens O, Deschenes M, Steben M, Belanger G, Tsoukas CM. Hepatitis C virus is related to progressive liver disease in human immunodeficiency virus-positive hemophiliacs and should be treated as an opportunistic infection. *Journal of Infectious Diseases.* 1999;179(5):1254–1258.

23. Soto B, Sanchez-Quijano A, Rodrigo L, et al. Human immunodeficiency virus infection modifies the natural history of chronic parenterally-acquired hepatitis C with an unusually rapid progression to cirrhosis. *Journal of Hepatology.* 1997;26(1):1–5.

24. Thomas DL, Shih JW, Alter HJ, et al. Effect of human immunodeficiency virus on hepatitis C virus infection among injecting drug users. *Journal of Infectious Diseases.* 1996;174(4):690–695.

25. Koff RS. Risks associated with hepatitis A and hepatitis B in patients with hepatitis C. *Journal of Clinical Gastroenterology.* 2001;33(1):20–26.

26. Zarski JP, Bohn B, Bastie A, et al. Characteristics of patients with dual infection by hepatitis B and C viruses. *Journal of Hepatology.* 1998;28(1):27–33.

27. Adinolfi LE, Gambardella M, Andreana A, Tripodi MF, Utili R, Ruggiero G. Steatosis accelerates the progression of liver damage of chronic hepatitis C patients and correlates with specific HCV genotype and visceral obesity. *Hepatology.* 2001;33(6):1358–1364.

28. Roudot-Thoraval F, Bastie A, Pawlotsky JM, Dhumeaux D. Epidemiological factors affecting the severity of hepatitis C virus-related liver disease: a French survey of 6,664 patients. *Hepatology.* 1997;26:485–490.

29. Gordon SC, Bayati N, Silverman AL. Clinical outcome of hepatitis C as a function of mode of transmission. *Hepatology.* 1998;28(2):562–567.

30. Gordon SC, Elloway RS, Long JC, Dmuchowski CF. The pathology of hepatitis C as a function of mode of transmission: blood transfusion vs. intravenous drug use. *Hepatology.* 1993;18(6):1338–1343.

31. Prati D, Capelli C, Zanella A, et al. Influence of different hepatitis C virus genotypes on the course of asymptomatic hepatitis C virus infection. *Gastroenterology.* 1996;110:178–183.

32. Wiley TE, Brown J, Chan J. Hepatitis C in African Americans: its natural history and histological progression. *American Journal of Gastroenterology.* 2002;97(3):700–706.

33. Gebo K, Jenckes M, Chander G, et al. (Agency for Healthcare Research and Quality). Management of Chronic Hepatitis C. Evidence Report/Technology Assessment No. 60. AHRQ Publication No. 02-E030. 2002.

34. Carithers RL, Jr., Marquardt A, Gretch DR. Diagnostic testing for hepatitis C. *Seminars in Liver Disease.* 2000;20(2):159–171.

35. Harris RP, Helfand M, Woolf SH, et al. Current methods of the third U.S. Preventive Services Task Force. *American Journal of Preventive Medicine.* 2001;20(3S):21–35.

36. Chou R, Clark EC, Helfand M. Screening for hepatitis C: systematic evidence review for the U.S. Preventive Services Task Force. Rockville, MD: Agency for Healthcare Research and Quality; 2003. Available at www.ahrq.gov/clinic.serfiles.htm.

37. Bellentani S, Pozzato G, Saccoccio G, 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(6):874–880.

38. Kaur S, Rybicki L, Bacon BR, Gollan JL, Rustgi VK, Carey WD. Performance characteristics and results of a large-scale screening program for viral hepatitis and risk factors associated with exposure to viral hepatitis B and C: results of the National Hepatitis Screening Survey. National Hepatitis Surveillance Group. *Hepatology.* 1996;24(5):979–986.

39. Cheung RC. Epidemiology of hepatitis C virus infection in American veterans. *American Journal of Gastroenterology.* 2000;95(3):740–747.

40. Austin GE, Jensen B, Leete J, et al. Prevalence of hepatitis C virus seropositivity among hospitalized US veterans. *American Journal of the Medical Sciences.* 2000;319(6):353–359.

41. Gore SM, Bird AG, Cameron SO, Hutchinson SJ, Burns SM, Goldberg DJ. Prevalence of hepatitis C in prisons: WASH-C surveillance linked to self-reported risk behaviours. *QJM.* 1999;92:25–32.

42. Prefontaine RG, Chaudhary RK, Mathias RG. Analysis of risk factors associated with hepatitis B and C infections in correctional institutions in British Columbia. *Canadian Journal of Infectious Disease.* 1994;5:153–156.

43. Roy E, Haley N, Leclerc P, Boivin JF, Cedras L, Vincelette J. Risk factors for hepatitis C virus infection among street youths. *CMAJ.* 2001;165(5):557–560.

44. Osmond DH, Padian NS, Sheppard HW, Glass S, Shiboski SC, Reingold A. Risk factors for hepatitis C virus seropositivity in heterosexual couples. *JAMA.* 1993;269:361–365.

45. Zylberberg H, Thiers V, Lagorce D, et al. Epidemiological and virological analysis of couples infected with hepatitis C virus. *Gut.* 1999;45(1):112–116.

46. Magriples U, Bernstein P, Snyder E, Copel JA. Can risk factor screening predict hepatitis C antibody reactivity? *American Journal of Perinatology.* 1998;15(6):395–398.

47. Neal KR, Jones DA, Killey D, James V. Risk factors for hepatitis C virus infection. A case-control study of blood donors in the Trent Region (UK). *Epidemiology & Infection.* 1994;112(3):595–601.

48. Kaldor JM, Archer GT, Buring ML, et al. Risk factors for hepatitis C virus infection in blood donors: a case-control study. *Medical Journal of Australia.* 1992;157(4):227–230.

49. Gunn RA, Murray PJ, Ackers ML, Hardison WG, Margolis HS. Screening for chronic hepatitis B and C virus infections in an urban sexually transmitted disease clinic: rationale for integrating services. *Sexually Transmitted Diseases.* 2001;28(3):166–170.

50. Stary A, Kopp W, Hofmann H, Heller-Vitouch C, Kunz C. Seroepidemiologic study of hepatitis C virus in sexually transmitted disease risk groups. *Sexually Transmitted Diseases.* 1992;19(5):252–258.

51. Weinstock HS, Bolan G, Reingold AL, Polish LB. Hepatitis C virus infection among patients attending a clinic for sexually transmitted diseases. *JAMA.* 1993;269:392–394.

52. Bell J, Batey RG, Farrell GC, Crewe EB, Cunningham AL, Byth K. Hepatitis C virus in intravenous drug users. *Medical Journal of Australia.* 1990;153(5):274–276.

53. Villano SA, Vlahov D, Nelson KE, Lyles CM, Cohn S, Thomas DL. Incidence and risk factors for hepatitis C among injection drug users in Baltimore, Maryland. *Journal of Clinical Microbiology.* 1997;35(12):3274–3277.

54. Patrick DM, Tyndall MW, Cornelisse PG, et al. Incidence of hepatitis C virus infection among injection drug users during an outbreak of HIV infection. *CMAJ.* 2001;165(7):889–895.

55. Alter MJ, Hadler SC, Judson FN, et al. Risk factors for acute non-A, non-B hepatitis in the United States and association with hepatitis C virus infection. *JAMA.* 1990;264(17):2231–2235.

56. Alter MJ. Epidemiology of hepatitis C. *Hepatology.* 1997;26(3 Suppl 1):62S–65S.

57. Alter MJ, Coleman PJ, Alexander WJ, et al. Importance of heterosexual activitiy in the transmission of hepatitis B and non-A, non-B hepatitis. *JAMA.* 1989;262(9):1201–1205.

58. Salleras L, Bruguera M, Vidal J, et al. Importance of sexual transmission of hepatitis C virus in seropositive pregnant women: a case-control study. *Journal of Medical Virology.* 1997;52:164–167.

59. Feldman JG, Minkoff H, Landesman S, Dehovitz J. Heterosexual transmission of hepatitis C, hepatitis B, and HIV-1 in a sample of inner city women. *Sexually Transmitted Diseases.* 2000;27(6):338–342.

60. Thomas DL, Zenilman JM, Alter HJ, et al. Sexual transmission of hepatitis C virus among patients attending sexually transmitted diseases clinics in Baltimore—an analysis of 309 sex partnerships. *Journal of Infectious Diseases.* 1995;171(4):768–775.

61. Terrault NA. Sexual activity as a risk factor for hepatitis C. *Hepatology.* 2002;36:S99–S105.

62. Akahane Y, Kojima M, Sugai Y, et al. Hepatitis C virus infection in spouses of patients with type C chronic liver disease. *Annals of Internal Medicine.* 1994;120(9):748–752.

63. Kao JH, Chen PJ, Yang PM, et al. Intrafamilial transmission of hepatitis C virus: the important role of infections between spouses. *Journal of Infectious Diseases.* 1992;166:900–903.

64. Kumar RM. Interspousal and intrafamilial transmission of hepatitis C virus: a myth or a concern? *Obstetrics & Gynecology.* 1998;91(3):426–431.

65. Seeff LB, Alter HJ. Spousal transmission of the hepatitis C virus? *Annals of Internal Medicine.* 1994;120(9):807–809.

66. Shev S, Widell A, Bergstrom T, Hermodsson S, Lindholm A, Norkrans G. Herpes simplex virus-2 may increase susceptibility of the sexual transmission of hepatitis C. *Sexually Transmitted Diseases.* 1995;22(4):210–216.

67. Anonymous. National Institutes of Health consensus development conference statement: Management of hepatitis C: 2002: June 10–12, 2002, revisions made September 12, 2002. http://consensus.nih.gov/cons/116/091202116cdc_statement.htm (accessed 11/12/03) ed: National Institutes of Health; 2002.

68. Schreiber GB, Busch MP, Kleinman SH, Korelitz JJ. The risk of transfusion-transmitted viral infections. The Retrovirus Epidemiology Donor Study. *New England Journal of Medicine.* 1996;334(26):1685–1690.

69. Booth JCL, O'Grady J, Neuberger J. Clinical guidelines on the management of hepatitis C. *Gut.* 2001;49(Suppl 1):i1–i21.

70. Alter MJ. Prevention of spread of hepatitis C. *Hepatology.* 2002;36:S93–S98.

71. Haley RW, Fischer RP. Commercial tattooing as a potentially important source of hepatitis C infection. *Medicine.* 2001;80:134–151.

72. Balasekaran R, Bulterys M, Jamal MM, et al. A case-control study of risk factors for sporadic hepatitis C infection in the southwestern United States. *American Journal of Gastroenterology.* 1999;96(5):1341–1346.

73. Silverman AL, Sekhon JS, Saginaw SJ, Wiedbrauk D, Balasubramaniam M, Gordon SC. Tattoo application is not associated with an increased risk for chronic viral hepatitis. *American Journal of Gastroenterology.* 2000;95(5):1312–1315.

74. Conry-Cantilena C, Vanraden M, Gibble J, et al. Routes of infection, viremia, and liver disease in blood donors found to have hepatitis C virus infection. *New England Journal of Medicine.* 1996;334:1691–1696.

75. Murphy EL, Bryzman S, Williams AE, et al. Demographic determinants of hepatitis C virus seroprevalence among blood donors. *Jama.* 1996;275(13):995–1000.

76. Rosman AS, Waraich A, Galvin K, Casiano J, Paronetto F, Lieber CS. Alcoholism is associated with hepatitis C but not hepatitis B in an urban population. *American Journal of Gastroenterology.* 1996;91(3):498–505.

77. Yawn B, Wollan P, Gazzuola L, Kim WR. Diagnosis and 10-year follow-up of a community-based hepatitis C cohort. *Journal of Family Practice.* 2002;51(2):135–140.

78. Lapane KL, Jakiche AF, Sugano D, Weng CS, Carey WD. Hepatitis C infection risk analysis: who should be screened? Comparison of multiple screening strategies based on the National Hepatitis Surveillance Program. *American Journal of Gastroenterology.* 1998;93(4):591–596.

79. Flamm SL, Parker RA, Chopra S. Risk factors associated with chronic hepatitis C virus infection: limited frequency of an unidentified source of transmission. *American Journal of Gastroenterology.* 1998;93(4):597–600.

80. Colin C, Lanoir D, Touzet S, et al. Sensitivity and specificity of third-generation hepatitis C virus antibody detection assays: an analysis of the literature. *Journal of Viral Hepatitis.* 2001;8(2):87–95.

81. Uyttendaele S, Claeys H, Mertens W, Verhaert H, Vermylen C. Evaluation of third-generation screening and confirmatory assays for HCV antibodies. *Vox Sanguinis.* 1994;66(2):122–129.

82. Stuyver L, Claeys H, Wyseur A, et al. Hepatitis C virus in a hemodialysis unit: molecular evidence for nosocomial transmission. *Kidney International.* 1996;49(3):889–895.

83. Wolff C, Kleesiek K, Petersen N, Beyer J. Hepatitis C viremia in German blood donors: serum alanine aminotransferase is not a valid marker for screening. *Transfusion.* 1994;34(4):361–362.

84. Lavanchy D, Steinmann J, Moritz A, Frei PC. Evaluation of a new automated third-generation anti-HCV enzyme immunoassay. *Journal of Clinical Laboratory Analysis.* 1996;10(5):269–276.

85. Courouce AM, Janot C. Development of screening and confirmation tests for antibodies to hepatitis C virus. *Current Studies in Hematology & Blood Transfusion.* 1994(61):36–48.

86. Courouce AM, Barin F, Botte C, et al. A comparative evaluation of the sensitivity of seven anti-hepatitis C virus screening tests. *Vox Sanguinis.* 1995;69(3):213–216.

87. Huber KR, Sebesta C, Bauer K. Detection of common hepatitis C virus subtypes with a third-generation enzyme immunoassay. *Hepatology.* 1996;24(3):471–473.

88. Busch MP, Watanabe KK, Smith JW, Hermansen SW, Thomson RA. False-negative testing errors in routine viral marker screening of blood donors. For the Retrovirus Epidemiology Donor Study. *Transfusion.* 2000;40(5):585–589.

89. Prince AM, Scheffel JW, Moore B. A search for hepatitis C virus polymerase chain reaction-positive but seronegative subjects among blood donors with elevated alanine aminotransferase. *Transfusion.* 1997;37(2):211–214.

90. Anonymous. Guidelines for laboratory testing and result reporting of antibody to hepatitis C virus. *Morbidity & Mortality Weekly Report Recommendations & Reports.* 2003;52(RR-3):1–16.

91. Alberti A, Noventa F, Benvegnu L, Boccato S, Gatta A. Prevalence of liver disease in a population of asymptomatic persons with hepatitis C virus infection. *Annals of Internal Medicine.* 2002;137:961–974.

92. Rodger AJ, Jolley D, Thompson SC, Lanigan A, Crofts N. The impact of diagnosis of hepatitis C virus on quality of life. *Hepatology.* 1999;30(5):1299–1301.

93. Coughlan BM, Sheehan JD, Carr A, Cockram AM, Crowe JP. Evaluation of a brief group-based psychological/educational (psych/ED) treatment programme for women with an iatrogenic hepatitis C virus (HCV) infection. *Gastroenterology.* 2001;129(Suppl 1):A568.

94. Gebo KA, Herlong HF, Torbenson MS, et al. Role of liver biopsy in management of chronic hepatitis C: a systematic review. *Hepatology.* 2002;36:S161–S172.

95. Lauer GM, Walker, B. Medical Progress: Hepatitis C Virsus Infection. *New England Journal of Medicine.* 2001;345(1):41–52.

96. Anonymous. EASL International Consensus Conference on Hepatitis C. Paris, 26–28 February 1999, Consensus Statement. European Association for the Study of the Liver. *Journal of Hepatology.* 1999;30(5):956–961.

97. Booth JC, Brown JL, Thomas HC. The management of chronic hepatitis C virus infection. *Gut.* 1995;37(4):449–454.

98. Galmiche JP. French consensus conference on hepatitis C: screening and treatment. *Gut.* 1998;42(6):892–898.

99. Bacon BR. Treatment of patients with hepatitis C and normal serum aminotransferase levels. *Hepatology.* 2002;36:S179–S184.

100. Muir AJ, Provenzale D. A descriptive evaluation of eligibility for therapy among veterans with chronic hepatitis C virus infection. *Journal of Clinical Gastroenterology.* 2002;34(3):268–271.

101. Cawthorne CH, Rudat KR, Burton MS, et al. Limited success of HCV antiviral therapy in United States veterans. *American Journal of Gastroenterology.* 2002;97(1):149–155.

102. Falck-Ytter Y, Kale H, Mullen KD, Sarbah SA, Sorescu L, McCullough AJ. Surprisingly small effect of antiviral treatment in patients with hepatitis C. *Annals of Internal Medicine.* 2002;136(4):288–292.

103. Bravo AA, Sheth SG, Chopra S. Liver biopsy. *New England Journal of Medicine.* 2001;344(7):495–500.

104. Garcia-Tsao G. Outpatient liver biopsy: how safe is it? *Annals of Internal Medicine.* 1993;118(2):150–152.

105. Froehlich F, Lamy L, Fried M, Gonvers JJ. Practice and complications of liver biopsy. *Digestive Diseases and Sciences.* 1993;38(8):1480–1484.

106. Janes CH, Lindor KD. Outcomes of patients hospitalized for complications after outpatient liver biopsy. *Annals of Internal Medicine.* 1993;118:96–98.

107. Gilmore IT, Burroughs A, Murray-Lyon IM, Williams R, Jenkins D, Hopkins A. Indications, methods, and outcomes of percutaneous liver biopsy in England and Wales. *Gut.* 1995;36:437–441.

108. Cadranel JF, Rufat P, Degos F. Practices of liver biopsy in France: results of a prospective nationwide survey. *Hepatology.* 2000;32:477–481.

109. McGill DB, Rakela J, Zinsmeister AR, Ott BJ. A 21-year experience with major hemorrhage after percutaneous liver biopsy. *Gastroenterology.* 1990;99:1396–1400.

110. Vautier G, Scott B, Jenkins D. Liver biopsy: blind or guided? *BMJ.* 1994;309:1455–1456.

111. Saadeh S, Cammell G, Carey WD, Younossi Z, Barnes D, Easley K. The role of liver biopsy in chronic hepatitis C. *Hepatology.* 2001;33:196–200.

112. Farrell RJ, Smiddy PF, Pilkington RM, et al. Guided versus blind liver biopsy for chronic hepatitis C: clinical benefits and costs. *Journal of Hepatology.* 1999;30:580–587.

113. Pasha T, Gabriel S, Therneau T, Dickson ER, Lindor KD. Cost-effectiveness of ultrasound-guided liver biopsy. *Hepatology.* 1998;27(5):1220–1226.

114. Caturelli E, Giacobbe A, Facciorusso D, et al. Percutaneous biopsy in diffuse liver disease: increasing diagnostic yield and decreasing complication rate by routine ultrasound assessment of puncture site. *American Journal of Gastroenterology.* 1996;91(7):1318–1321.

115. Lindor KD, Bru C, Jorgensen RA, et al. The role of ultrasonography and automatic-needle biopsy in outpatient percutaneous liver biopsy. *Hepatology.* 1996;23:1079–1083.

116. Pawlotsky JM. Use and interpretation of virological tests for hepatitis C. *Hepatology.* 2002;36:S65–S73.

117. Hoofnagle JH, di Bisceglie AM. The treatment of chronic viral hepatitis. *New England Journal of Medicine.* 1997;336(5):347–356.

118. Poynard T, Leroy V, Cohard M, et al. Meta-analysis of interferon randomized trials in the treatment of viral hepatitis C: effects of dose and duration. *Hepatology.* 1996;24(4):778–789.

119. Kjaergard LL, Krogsgaard K, Gluud C. Interferon alfa with or without ribavirin for chronic hepatitis C: systematic review of randomised trials. *BMJ.* 2001;323(7322):1151–1155.

120. Chander G, Sulkowski MS, Jenckes MW, et al. Treatment of chronic hepatitis C: a systematic review. *Hepatology.* 2002;36:S135–S144.

121. Shepherd J, Waugh N, Hewitson P. Combination therapy (interferon alfa and ribavirin) in the treatment of chronic hepatitis C: a rapid and systematic review. *Health Technology Assessment.* 2000;4(33):1–67.

122. Fried MW, Shiffman ML, Reddy KR, et al. Peginterferon Alfa-2a plus ribavirin for chronic hepatitis C virus infections. *New England Journal of Medicine.* 2002;347(13):975–982.

123. Manns MP, McHutchison JG, Gordon SC, 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(9286):958–965.

124. Glue P, Rouzier-Panis R, Raffanel C, et al. A dose-ranging study of pegylated interferon alfa-2b and ribavirin in chronic hepatitis C. The Hepatitis C Intervention Therapy Group. *Hepatology.* 2000;32(3):647–653.

125. Heathcote EJ, Shiffman ML, Cooksley WG, et al. Peginterferon alfa-2a in patients with chronic hepatitis C and cirrhosis. *New England Journal of Medicine.* 2000;343(23):1673–1680.

126. Lindsay KL, Trepo C, Heintges T, et al. A randomized, double-blind trial comparing pegylated interferon alfa-2b to interferon alfa-2b as initial treatment for chronic hepatitis C. *Hepatology.* 2001;34(2):395–403.

127. Reddy KR, Wright TL, Pockros PJ, et al. Efficacy and safety of pegylated (40-kd) interferon alpha-2a compared with interferon alpha-2a in noncirrhotic patients with chronic hepatitis C. *Hepatology.* 2001;33(2):433–438.

128. Zeuzem S, Feinman SV, Rasenack J, et al. Peginterferon alfa-2a in patients with chronic hepatitis C. *New England Journal of Medicine.* 2000;343(23):1666–1672.

129. Nishiguchi S, Shiomi S, Nakatani S, et al. Prevention of hepatocellular carcinoma in patients with chronic active hepatitis C and cirrhosis. *Lancet.* 2001;357(9251):196–197.

130. Bernardinello E, Cavalletto L, Chemello L, et al. Long-term clinical outcome after beta-interferon therapy in cirrhotic patients with chronic hepatitis C. TVVH Study Group. *Hepato Gastroenterology.* 1999;46(30):3216–3222.

131. Harris HE, Ramsay ME, Andrews N, Eldridge KP. Clinical course of hepatitis C virus during the first decade of infection: cohort study. *BMJ.* 2002;324(7335):450–453.

132. Seeff LB, Miller RN, Rabkin CS, et al. 45-year follow-up of hepatitis C virus infection in healthy young adults. *Annals of Internal Medicine.* 2000;132(2):105–111.

133. Davis Gl, Balart LA, Schiff ER, et al. Assessing health-related quality of life in chronic hepatitis C

using the Sickness Impact Profile. *Clinical Therapeutics.* 1994;16(2):334–343.

134. Zarski JP, Leroy V. Counselling patients with hepatitis C. *Journal of Hepatology.* 1999;31(Suppl 1):136–140.

135. Keeffe EB, Iwarson S, McMahon BJ, et al. Safety and immunogenicity of hepatitis A vaccine in patients with chronic liver disease. *Hepatology.* 1998;27(3):881–886.

136. Vento S, Garofano T, Renzini C, et al. Fulminant hepatitis associated with hepatitis A virus superinfection in patients with chronic hepatitis C. *New England Journal of Medicine.* 1998;338(5):286–290.

137. Hasle G, Hoel T, Jensenius M. Mortality of hepatitis A in adults with hepatitis C antibodies. *Lancet.* 1998;351:1888.

138. Mele A, Tosti ME, Stroffolini T. Hepatitis associated with hepatitis A superinfection in patients with chronic hepatitis C. *New England Journal of Medicine.* 1998;338(24):1771–1772.

139. Nalpas B, Martin S, Fontaine H, Fabbro-Peray P, Brechot C, Pol S. Impact of medical recommendations on alcohol consumption in HCV positive patients. *Journal of Hepatology.* 2001;35(2):312–313.

140. Ompad DC, Fuller CM, Vlahov D, Thomas DL, Strathdee SA. Lack of behavior change after disclosure of hepatitis C virus infection among young injection drug uses in Baltimore, Maryland. *Clinical Infectious Diseases.* 2002;35(7):783–788.

141. Ikeda K, Saitoh S, Arase Y, et al. Effect of interferon therapy on hepatocellular carcinogenesis in patients with chronic hepatitis type C: A long-term observation study of 1,643 patients using statistical bias correction with proportional hazard analysis. *Hepatology.* 1999;29(4):1124–1130.

142. Bernstein D, Kleinman L, Barker CM, Revicki DA, Green J. Relationship of health-related quality of life to treatment adherence and sustained response in chronic hepatitis C patients. *Hepatology.* 2002;35(3):704–708.

143. Bonkovsky HL, Woolley JM. Reduction of health-related quality of life in chronic hepatitis C and improvement with interferon therapy. The Consensus Interferon Study Group. *Hepatology.* 1999;29(1):264–270.

144. McHutchison JG, Ware JE, Jr., Bayliss MS, et al. The effects of interferon alpha-2b in combination with ribavirin on health related quality of life and work productivity. *Journal of Hepatology.* 2001;34(1):140–147.

145. Strader DB. Understudied populations with hepatitis C. *Hepatology.* 2002;36:S226–S236.

146. Schiff ER, de Medina M, Kahn RS. New perspectives in the diagnosis of hepatitis C. *Seminars in Liver Disease.* 1999;19(Suppl 1):3–15.

147. Saito M, Hasegawa A, Kashiwakuma T, et al. Performance of an enzyme-linked immunosorbent assay system for antibodies to hepatitis C virus with two new antigens (c11/c7). *Clinical Chemistry.* 1992;38(12):2434–2439.

148. Brown D, Powell L, Morris A, et al. Improved diagnosis of chronic hepatitis C virus infection by detection of antibody to multiple epitopes: confirmation by antibody to synthetic oligopeptides. *Journal of Medical Virology.* 1992;38(3):167–171.

149. Damen M, Zaaijer H, Cuypers HT, et al. Reliability of the third-generation recombinant immunoblot assay for hepatitis C virus. *Transfusion.* 1995;35(9):745–749.

150. Dow BC, Buchanan I, Munro H, et al. Relevance of RIBA-3 supplementary test to HCV PCR positivity and genotypes for HCV confirmation of blood donors. *Journal of Medical Virology.* 1996;49(2):132–136.

151. Pawlotsky JM, Bastie A, Pellet C, et al. Significance of indeterminate third-generation hepatitis C virus recombinant immunoblot assay. *Journal of Clinical Microbiology.* 1996;34(1):80–83.

152. Icardi G, Ansaldi F, Bruzzone BM, et al. Novel approach to reduce the hepatitis C virus (HCV) window period: clinical evaluation of a new enzyme-linked immunosorbent assay for HCV core antigen. *Journal of Clinical Microbiology.* 2001;39(9):3110–3114.

153. Widell A, Molnegren V, Pieksma F, Calmann M, Peterson J, Lee SR. Detection of hepatitis C core antigen in serum or plasma as a marker of hepatitis C viraemia in the serological window-phase. *Transfusion Medicine.* 2002;12(2):107–113.

154. Dore GJ, Kaldor J, McCaughan GW. Systematic review of role of polymerase chain reaction in

defining infectiousness among people infected with hepatitis C virus. *BMJ.* 1997;315:333–341.

155. Alberti A, Morsica G, Chemello L, Cavalletto D, Noventa F, Pontisso P, et al. Hepatitus C viraemia and liver disease in symptom-free individuals with anti-HCV. *Lancet.* 1992;340:697–699.

156. Prieto M, Olaso V, Verdu C, et al. Does the healthy hepatitis C virus carrier state really exist? An analysis using polymerase chain reaction. *Hepatology.* 1995;22(2):413–417.

157. Montalto G, Zignego AL, Ruggeri MI, et al. Serum HCV-RNA and liver histologic findings in patients with long-term normal transaminases. *Digestive Diseases & Sciences.* 1997;42(8):1703–1707.

158. Poynard T, Ratziu V, Charlotte F, Goodman Z, McHutchison J, Albrecht J. Rates and risk factors of liver fibrosis progression in patients with chronic hepatitis C. *Journal of Hepatology.* 2001;34(5):730–739.

159. Puoti C, Stati T, Magrini A. Serum HCV RNA titer does not predict the severity of liver damage in HCV carriers with normal aminotransferase levels. *Liver.* 1999;19(2):104–109.

160. Shakil AO, Conry-Cantilena C, Alter HJ, et al. Volunteer blood donors with antibody to hepatitis C virus: clinical, biochemical, virologic, and histologic features. *Annals of Internal Medicine.* 1995;123:330–337.

161. McCormick SE, Goodman ZD, Maydonovitch CL, Sjogren MH. Evaluation of liver histology, ALT elevation, and HCV RNA titer in patients with chronic hepatitis C. *American Journal of Gastroenterology.* 1996;91(8):1516–1522.

162. Reichard O, Norkrans G, Fryden A, Braconier JH, Sonnerborg A, Weiland O. Comparison of 3 quantitative HCV RNA assays—accuracy of baseline viral load to predict treatment outcome in chronic hepatitis C. *Scandinavian Journal of Infectious Diseases.* 1998;30(5):441–446.

163. Yokosuka O, Kojima H. Imazeki F. Tagawa M. Saisho H. Tamatsukuri S. Omata M. Spontaneous negativation of serum hepatitis C virus RNA is a rare event in type C chronic liver diseases: analysis of HCV RNA in 320 patients who were followed for more than 3 years. *Journal of Hepatology.* 1999;31(3):394–399.

164. Zaaijer HL, Cuypers HT, Reesink HW, Winkel IN, Gerken G, Lelie PN. Reliability of polymerase chain reaction for detection of hepatitis C virus. *Lancet.* 1993;341(8847):722–724.

165. Pawlotsky JM. Measuring hepatitis C viremia in clinical samples: can we trust the assays? *Hepatology.* 1997;26(1):1–4.

166. Long GS, Bacon BR, Bisceglie AM. Interpreting serologic tests for hepatitis C virus infection: balancing cost and clarity. *Cleveland Clinic Journal of Medicine.* 1996;63(5):264–268.

167. Gretch DR. Diagnostic tests for hepatitis C. *Hepatology.* 1997;26(3 Suppl 1):43S–47S.

168. Sakugawa H, Nakasone H, Nakayoshi T, et al. High proportion of false positive reactions among donors with anti-HCV antibodies in a low prevalence area. *Journal of Medical Virology.* 1995;46(4):334–338.

169. Ishak K, Baptista A, Bianchi L, et al. Histological grading and staging of chronic hepatitis. *Journal of Hepatology.* 1995;22:696–699.

170. Bedossa P, Poynard T. An algorithm for the grading of activity in chronic hepatitis C. The METAVIR Cooperative Study Group. *Hepatology.* 1996;24(2):289–293.

171. Knodell RG, Ishak KG, Black WC, et al. Formulation and application of a numerical scoring system for assessing histological activity in asymptomatic chronic active hepatitis. *Hepatology.* 1981;1:431–435.

172. Jonas MM. Challenges in the treatment of hepatitis C in children. *Clinics in Liver Disease.* 2001;5(4):1063–1071.

173. Zanetti AR, Tanzi E, Paccagnini S, et al. Mother-to-infant transmission of hepatitis C virus. Lombardy Study Group on Vertical HCV Transmission. *Lancet.* 1995;345(8945):289–291.

174. Tajiri H, Miyoshi Y, Funada S, et al. Prospective study of mother-to-infant transmission of hepatitis C virus. *Pediatric Infectious Disease Journal.* 2001;20(1):10–14.

175. 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(3):751–755.

176. Gibb DM, Goodall RL, Dunn DT, et al. Mother-to-child transmission of hepatitis C virus: evidence for preventable peripartum transmission. *Lancet.* 2000;356(9233):904–907.

177. Sanchez-Quijano A, Andreu J, Gavilan F, et al. Influence of human immunodeficiency virus type 1 infection on the natural course of chronic parenterally acquired hepatitis C. *European Journal of Clinical Microbiology & Infectious Diseases.* 1995;14(11):949–953.

178. Furusyo N, Hayashi J, Kanamoto-Tanaka Y, et al. Liver damage in hemodialysis patients with hepatitis C virus viremia: a prospective 10-year study. *Digestive Diseases & Sciences.* 2000;45(11):2221–2228.

179. Rostaing L, Rumeau JL, Cisterne JM, Izopet J, Chabannier MH, Durand D. Liver histology in renal transplant patients after more than 10 years of hepatitis C virus infection. *Transplantation Proceedings.* 1996;28(5):2836–2837.

180. Kliem V, van den Hoff U, Brunkhorst R, et al. The long-term course of hepatitis C after kidney transplantation. *Transplantation.* 1996;62(10):1417–1421.

181. Anonymous. National Institutes of Health Consensus Development Conference Panel statement: management of hepatitis C. *Hepatology.* 1997;26(3 Suppl 1):2S–10S.

Appendix

Definitions

This section summarizes terminology describing the tests used to identify patients with HCV infection, the results of these tests (Appendix Table), and the response to treatment. The Centers for Disease Control and Prevention (CDC) has recently published detailed guidelines for performing laboratory testing and reporting results of anti-HCV and supplemental testing.[90]

Enzyme-linked immunoassay (ELISA) or enzyme immunoassay (EIA): The ELISA (also referred to as EIA) detects antibodies against recombinant HCV antigens. "First generation" ELISAs used a single antigen; later tests added additional antigens.[146–148] Second and third-generation tests are both in standard use. Because of concerns about false-positive tests, particularly in low-prevalence populations (such as blood donors or asymptomatic adults), the CDC has recommended confirming positive ELISA results with a supplemental test (recombinant immunoblot assay or polymerase chain reaction), unless the signal-to-cut-off ratio is above a predetermined threshold that has been shown to confirm positive more than 95% of the time.[90]

ELISA is the least expensive diagnostic test for HCV infection, with an average charge of about $60.00.[34]

Recombinant immunoblot assay (RIBA): RIBA is a supplemental test that also detects antibodies against HCV antigens. In these assays, multiple HCV antigens are individually displayed on a nitrocellulose strip as bands. Positive RIBA results have at least 2 reactive bands; indeterminate results have 1 reactive band. Because positive RIBA results require reactivity to more than 1 HCV antigen, they are considered more specific (but not more sensitive) than ELISA for

Appendix Table. Results of Screening Tests for Hepatitis C Virus and Usual Interpretation

ELISA Results	RIBA Results	PCR Results	Interpretation
Positive	Positive or indeterminate	Positive	Active or chronic HCV infection
Positive	Positive	Negative	Cleared HCV infection if PCR persistently negative
Positive	Negative, intermediate, or not performed	Negative	Cleared HCV infection or false-positive results on ELISA
Positive	Negative	Not usually done if RIBA results are negative	False-positive results on ELISA
Negative	Not performed if ELISA results are negative	Not usually done if ELISA results are negative (unless suspicion for acute infection is high)	No evidence of past exposure to HCV
Negative	Not performed if ELISA results are negative	Positive (test is not usually done in clinical settings unless suspicion for infection is high)	Early (<7–8 wk) HCV infection or false-negative results

ELISA = enzyme-linked immunoassay; HCV = hepatitis C virus; PCR = polymerase chain reaction; RIBA = recombinant immunoblot assay

past HCV infection, and are used to confirm positive ELISA results in low-prevalence populations.[34] However, RIBA is not an independent gold standard for ELISA because the 2 tests use similar antigens to detect anti-HCV antibodies.

Currently available third-generation RIBA are thought to be more specific than earlier-generation tests because they produce fewer indeterminate results.[149] The interpretation of indeterminate RIBA results remains uncertain.[90,150,151] The relative proportion of RIBA-positive, RIBA-indeterminate, and RIBA-negative test results in patients with positive results on ELISA varies according to the patients studied.

The RIBA is typically 2 to 3 times more expensive than ELISA; usual charges are about $140.00.[34]

HCV core antigen testing: Recently developed tests to detect HCV core antigen may aid in diagnosing acute infection in the "window period" before HCV antibodies develop.[152,153] The role of HCV core antigen testing in screening has not yet been established.

Reverse transcription polymerase chain reaction (RT-PCR or PCR): This is a laboratory method used to detect circulating HCV RNA in blood. A PCR can be quantitative or qualitative, and under optimal conditions qualitative PCR can detect 100 international units (IU)/mL or less of circulating virus.[34,116] Because the absence of viremia in patients who test positive for anti-HCV-antibodies is associated with little or no risk for HCV infection[154] or complications related to chronic HCV infection, sustained PCR-detected viremia has become the gold standard for chronic HCV infection.[6,132,155–157] In patients who have positive results on PCR, the degree of viremia correlates poorly with degree of liver damage,[157–161] although these results may help predict the likelihood of response to treatment.[162]

Strict quality control is necessary for PCR testing to be reliable. False negative test results can occur because some patients with active infection have intermittent viremia, and a small portion of patients with chronic HCV infection can become non-viremic, particularly if they develop hepatocellular cancer.[163–165] For this reason, repeat PCR resting is suggested in high-risk patients who are positive for anti-HCV antibodies but have negative results on initial PCR. False-positive PCR test results may also occur due to contamination of samples (11% in 1 early quality control study) but appear to be much less frequent since standardization of assay techniques.[164]

PCR testing is associated with charges of about $130.00 for a qualitative test and $200.00 for a quantitative test.[34]

False-positive ELISA results: Patients who have positive results on ELISA but negative results on RIBA or negative results on both RIBA and PCR are usually considered false-positive results (that is, they have no evidence of past or current HCV infection). False positive ELISA results may occur in patients with autoimmune diseases and in neonates born to mothers with chronic HCV infection, who frequently pass on antibodies to their children but usually do not pass on the virus.[34,116]

False-negative ELISA results: Patients who have negative results on ELISA but positive results on PCR are usually considered to have false-negative results. False-negatives results are probably most common very early after infection (it takes 6 to 8 weeks for third-generation-ELISAs to yield positive results vs. 2 to 3 weeks for PCR) or in patients who have an impaired immune system.[34]

Cleared or resolved HCV infection: Patients who have positive results on ELISA and RIBA but negative results on PCR on repeated testing are generally considered to have cleared or resolved HCV infection. This is usually not considered a false-positive finding because the positive RIBA test results provides specific evidence of past exposure to HCV.[166] Patients who have positive results on ELISA, indeterminate results on RIBA (or no RIBA performed), and negative results on PCR may either have false-positive results or have cleared their HCV infection. False-positive tests are more common in low-prevalence settings.[167,168]

Chronic or active HCV infection: Patients who have persistent positive results on PCR are said to have chronic HCV infection. Chronic infection may present with or without symptoms, abnormal aminotransferase levels, or abnormal biopsy findings. In this review, the term *asymptomatic chronic HCV infection* refers to patients who report no symptoms

of HCV infection. Like symptomatic patients, asymptomatic patients may or may not have abnormal biopsy results or aminotransferase levels.

Liver biopsy results: The Histologic Activity Index is used to grade histologic findings. The Knodell score and the METAVIR scoring system are common methods used to report the Histologic Activity Index.[169,170] The Knodell score is a semiquantitative scoring system in which fibrosis and portal, periportal, and lobular necrotic and inflammatory components are assessed separately and their coding values added. Maximum scores vary depending on exactly how the scores are totaled.[171] The METAVIR system reports both the inflammatory and the fibrosis scores using separate standardized scores for activity and fibrosis.[170]

Early responders: Patients with HCV infection who receive treatment and clear their viremia (viremia load undetectable by PCR) or have a significant response (usually defined as a 2-log drop in HCV RNA level) in the first few months of treatment are referred to as *early responders*. People who are not early responders (usually measured at 12 weeks of therapy) have a low chance of successful treatment and may not benefit from further therapy.[116] Normalization of aminotransferase levels (biochemical response) was reported in earlier trials of HCV treatment, but has been replaced by assessments of virologic status, which are thought to be more accurate predictors of successful treatment.

End-of-treatment responders: Patients with HCV infection who receive treatment, clear their viremia, and maintain this response until the end of treatment are referred to as *end-of-treatment responders.* Presence of HCV RNA at the end of treatment is highly predictive of relapse when therapy is stopped.[116]

Sustained responders or sustained virologic responders: Patients with HCV infection who receive treatment and clear their viremia and maintain this response 6 to 12 months after the completion of treatment are referred to as *sustained responders* or *sustained virologic responders.*

Nonresponders: Patients with HCV infection who do not clear their viremia during treatment are considered *nonresponders.*

Analytic Framework and Key Questions

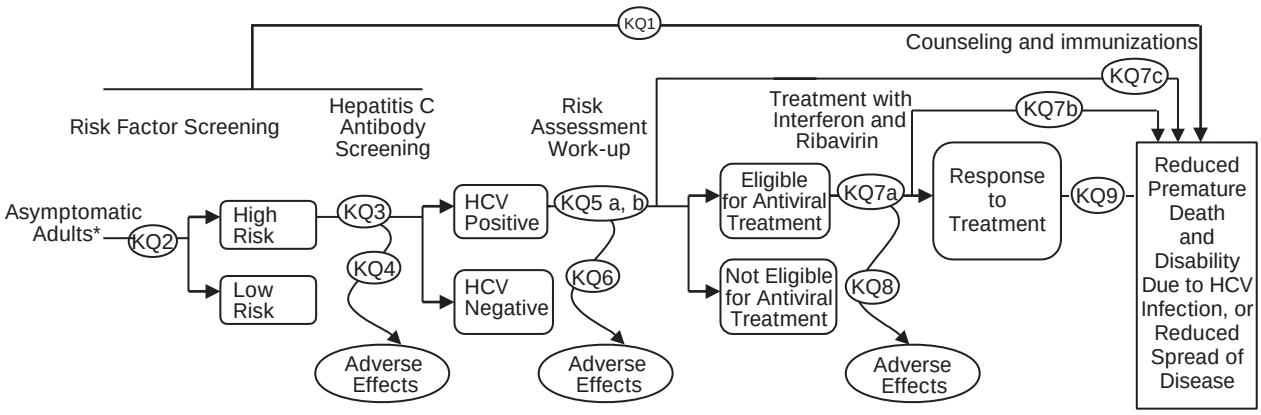
The analytic framework in the Appendix Figure indicates the strategy we used to evaluate screening for HCV infection in adults without known or suspected liver disease or abnormalities on liver function tests. The key questions, which guided our literature review, were determined in conjunction with liaisons from the U.S. Preventive Services Task Force.

The analytic framework shows the target samples, interventions, and intermediate and health outcome measures we examined. We narrowed the scope of the literature review after a preliminary search. We excluded children from the review because of the low prevalence of anti-HCV antibodies (0.2% to 0.4% in those 6 to 19 years old)[3] and the unclear safety and efficacy of treatment in this population.[172] We also excluded pregnant women because of unclear safety of treatment and insufficient evidence regarding ability to lower vertical transmission rates (estimated at approximately 5% in mothers without HIV infection).[173–176] We excluded other specific populations, such as patients who had received transplants, HIV-infected patients, and patients receiving hemodialysis patients. In these patients, screening test characteristics and natural history of HCV infection may differ from what is observed in the general population.[23, 177–180] In addition, these populations have generally been excluded from large trials of treatment and data regarding clinical outcomes are lacking. Patients with occupational exposures were also excluded because of clear consensus regarding screening after percutaneous exposures.[1]

Our review evaluated the screening strategy in which a second- or third-generation HCV ELISA is the initial test, with confirmatory RIBA. These are the screening tests that are currently in standard use for the diagnosis of current or resolved HCV infection.[90] PCR testing, aminotransferase testing, and liver biopsy were considered the standard work-up to determine presence of chronic HCV infection and eligibility for treatment in patients who tested positive for anti-HCV antibodies.

For treatment of chronic HCV infection, we focused on evidence regarding efficacy and safety

Appendix Figure 1. Screening for Hepatitis C: Analytic Framework*



* Excluding pregnant women, HIV positive persons, transplant recipients, and patients with renal failure.

KQ 1: Does screening for hepatitis C reduce the risk or rates of harm and premature death and disability?
KQ 2: Can clinical or demographic characteristics identify a subgroup of asymptomatic patients at higher risk for HCV infection?
KQ 3: What are the test characteristics of HCV antibody testing?
KQ 4: What is the predictive value of a positive screening test result, and what are the harms associated with screening for HCV infection?
KQ 5: a) What are the test characteristics of the work-up for active disease?
b) In patients found to be positive for hepatitis C virus antibody, what proportion of patients would qualify for treatment?
KQ 6: What are the harms associated with the work-up for active HCV disease?
KQ 7: a) How well does antiviral treatment reduce the rate of viremia, improve aminotransferase levels, and improve histology?
b) How well does antiviral treatment improve health outcomes in asymptomatic patients with hepatitis C?
c) How well do counseling and immunizations in asymptomatic patients with HCV infection improve clinical outcomes or prevent spread of disease?
KQ 8: What are the harms (including intolerance to treatment) associated with antiviral intervention?
KQ 9: Have improvements in intermediate outcomes (liver function tests, remission, histologic changes) been shown to reduce the risk or rate of harm from HCV infection?

of pegylated interferon with ribavirin, the treatment regimen found in good-quality trials to have the highest efficacy. Because this treatment regimen has been available for evaluation only a short time, we also reviewed evidence regarding the effect of other interferon-based treatment regimens on long-term clinical outcomes. Ribavirin alone, amantadine, and corticosteroids were not included because they have not been found to be efficacious.[1,98,181]

For outcomes, we were particularly interested in reviewing any literature on the benefit of early antiviral treatment of chronic HCV infection in asymptomatic patients. Clinical outcomes that we evaluated were mortality, end-stage liver disease, cirrhosis, and hepatocellular cancer. Quality of life outcomes were also evaluated. Intermediate outcomes were loss of detectable viremia, improvement in histologic findings, and normalization of aminotransferase levels. We also reviewed adverse outcomes from screening and treatment including side effects from treatment, adverse events from liver biopsy, and effects of diagnosing chronic HCV infection on quality of life.

Other reasons for screening for HCV infection might be to prevent spread of the disease or to identify those who might benefit from hepatitis A or B vaccination, alcohol cessation counseling, or

other interventions. We performed an additional literature search and review to identify potential benefits from screening that leads to these types of interventions in patients with chronic HCV.

Methods

Search Strategy

We searched the topic of HCV in the MEDLINE (1989 to July 2002, update search in February 2003) and the Cochrane Clinical Trials Registry (2002, Issue 2). We originally performed 3 MEDLINE searches, one for screening for HCV infection, one for work-up of HCV infection, and one for treatment of HCV infection. For screening, the medical subject headings (MeSH) *hepatitis C* and *hepacivirus* were combined with the terms *mass screening, hepatitis C antibodies, predictive value of tests,* and *sensitivity and specificity,* and the text words *antibody testing.* For work-up, the MeSH headings *hepatitis C* and *hepacivirus* were combined with the terms *ultrasonography, liver function tests, liver biopsy,* and *viral load.* For treatment, the MeSH headings *antiviral agents, interferons,* and *ribavarin* were combined with the terms *hepatitis C* and *hepacivirus.* We conducted a search for controlled studies of treatment of HCV infection in the Cochrane Library databases, using the phrase *hepatitis C* in title, abstract, or keywords combined with terms for clinical trials. We retrieved the complete reference list from a recent Agency for Healthcare Research and Quality evidence report commissioned by the National Institutes of Health to update its consensus statement on management of HCV infection.[33] Periodic hand searching of hepatology, gastroenterology, and major medical journals; review of the reference lists of retrieved articles; and suggestions from expert reviewers supplemented the electronic searches.

We performed an additional MEDLINE search in February 2003 on counseling on alcohol use, immunizations, and risky behaviors in patients with HCV infection. For this search, we combined the MeSH headings *hepatitis C, hepacivirus,* or *hepatitis C, chronic* with the MeSH headings *patient education, counseling, alcohol drinking, viral hepatitis vaccines, hepatitis A,* or *vaccination.*

One reader reviewed all English-language abstracts. Papers were selected for full review if they were about HCV infection, were relevant to key questions in the analytic framework, and met other inclusion criteria specific to the key questions. Reviews, policy statements, and other papers with contextual value were also obtained from the searches. Studies published as abstracts were not included in the search; although pertinent abstracts may be referred to in the text they are not included in evidence tables.

Inclusion Criteria

For all key questions, articles were limited to those that evaluated the general adult population with chronic HCV infection. We excluded studies that focused only on patients with end-stage liver disease, cirrhosis, or hepatocellular cancer. Although the population of interest was asymptomatic adults with chronic HCV infection who would be identified by screening, we included studies of patients with a broad spectrum of chronic HCV disease to get a picture of the benefits and adverse effects of screening and treatment in patients with different degrees of liver disease. Studies on persons with HCV who had undergone transplantation were excluded, as were studies of pregnant patients, children, or those with end-stage renal disease or HIV infection. Studies of non-human subjects were also excluded, and studies had to include original data. Foreign language papers were considered if they were clinical trials and an abstract was available in English. We searched for relevant systematic reviews for all key questions.

For individual key questions, additional inclusion criteria were as follows:

For key question 1, articles were included if they were clinical trials or observational studies that evaluated clinical outcomes in patients screened and not screened for HCV infection.

For key question 2, we included large observational studies that used appropriate statistical methods to assess associations between various risk factors and the presence of HCV infection. Representative smaller observational studies were also reviewed.

For key questions 3a, 3b, and 4, we included observational studies and systematic reviews that evaluated third-generation ELISA (the most recent generation) and used a credible, current reference standard (third-generation RIBA or PCR). We did not include studies that evaluated third-generation ELISA only in relationship to an earlier generation ELISA or performed the reference standard only in "discordant" samples from 2 screening tests. We also included data from large, good-quality observational studies on diagnostic test characteristics of second-generation ELISA.

For key question 5a, we included studies that evaluated the ability of blood tests to predict liver biopsy results, and performed liver biopsy as the reference standard.

For key question 5b, we included clinical trials and observational studies that reported the number of patients referred or considered for HCV treatment after a positive HCV antibody test, and that also provided detailed information about the reasons patients were considered ineligible for treatment.

For key question 6, we included observational studies that reported complications from percutaneous liver biopsy specifically in patients with chronic HCV infection. We also included representative large higher-quality observational studies of complications from percutaneous liver biopsy performed for a variety of indications.

For key questions 7a and 7b, we included controlled trials of antiviral treatment that evaluated relevant intermediate or clinical outcomes in treatment-naive samples. We included studies that evaluated pegylated interferon with or without ribavirin versus another treatment or placebo, and studies that evaluated non-pegylated interferon plus ribavirin compared to interferon alone or placebo. For question 7b, controlled trials of non-pegylated interferon without ribavirin were also included if they had more than 5 years of post-treatment follow-up and evaluated clinical or histologic outcomes. We reviewed clinical trials that were previously included in good-quality systematic reviews to ensure accuracy and reproducibility of the findings of the systematic reviews.

For key question 7c, we included controlled trials and observational studies that evaluated the effectiveness of counseling and immunizations in patients with HCV for improving clinical outcomes related to hepatitis A or B infection, alcohol use, or preventing spread of disease.

For key question 8, we included controlled antiviral trials and observational studies that reported adverse events in treatment-naive samples. We included studies of pegylated interferon with or without ribavirin versus another treatment or placebo and studies of nonpegylated interferon plus ribavirin versus another treatment or placebo.

For key question 9 we included controlled antiviral trials and observational studies in which long-term outcomes were stratified by intermediate responses to treatment.

For all key questions, we reviewed meta-analyses and systematic reviews when available.

Data Extraction

We used predefined criteria from the USPSTF to assess the internal validity of included systematic reviews, trials and observational studies, which we rated as good, fair, or poor. We also rated the applicability of each study to the population that would be identified by screening. The rating system was developed by the USPTF and is described in detail elsewhere.[35] For included trials and systematic reviews, we also abstracted information about setting, patients, interventions, and outcomes. For clinical trials, when possible we recorded the difference between the probability of a response in the treatment and control groups for each outcome studied. We evaluated the applicability of reviewed studies to the population likely to be identified by screening. We developed evidence tables for those key questions related to antiviral treatment of HCV infection (key questions 7a and 7b). We rated the overall body of evidence for each key question using the system developed by the USPTF.[35]

AHRQ Pub. No. 04-0534B
March 2004