Screening for Hepatitis C in Adults: Recommendation Statement

U.S. Preventive Services Task Force

Corresponding Author: Ned Calonge, MD, MPH, Chair, U.S. Preventive Services Task Force, c/o Program Director, USPSTF, Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, e-mail: uspstf@ahrq.gov.

This statement summarizes the U.S. Preventive Services Task Force (USPSTF) recommendations on screening for hepatitis C virus (HCV) infection based on the USPSTF's examination of evidence specific to asymptomatic persons for HCV testing and treatment. Explanations of the ratings and strength of overall evidence are given in Appendix A and Appendix B, respectively. The complete information on which this statement is based, including evidence tables and references, is available in the systematic evidence review[1] and in the summary article[2] on this topic, available through the USPSTF Web site (www.preventiveservices.ahrq.gov) and through

the National Guideline Clearinghouse™ (www.guideline.gov). The recommendation statement and summary article are also available from the Agency for Healthcare Research and Quality (AHRQ) Publications Clearinghouse in print through subscription to the *Guide to Clinical Preventive Services, Third Edition: Periodic Updates.* To order, contact the Clearinghouse at 1-800-358-9295, or e-mail ahrqpubs@ahrq.gov.

Recommendations made by the USPSTF are independent of the U.S. Government. They should not be construed as an official position of AHRQ or the U.S. Department of Health and Human Services.

This recommendation first appeared in *Ann Intern Med*. 2004;140:462-464.

Summary of Recommendations

The USPSTF recommends against routine screening for hepatitis C virus (HCV) infection in asymptomatic adults who are not at increased risk (general population) for infection. D recommendation.

The USPSTF found good evidence that screening with available tests can detect HCV infection in the general population. The prevalence of HCV infection in the general population is low, and most who are infected do not develop cirrhosis or other major negative health outcomes. There is no evidence that screening for HCV infection leads to improved long-term health outcomes, such as decreased cirrhosis, hepatocellular cancer, or mortality. Although there is good evidence that anti-viral therapy improves intermediate outcomes, such as viremia, there is limited evidence that such treatment improves long-term health outcomes. The current treatment regimen is long and costly and is associated with a high patient dropout rate due to adverse effects. Potential harms of screening include unnecessary biopsies and labeling, although there is limited evidence to determine the magnitude of these harms. As a result, the USPSTF concluded that the potential harms of screening for HCV infection in adults who are not at increased risk for HCV infection are likely to exceed potential benefits.

The USPSTF found insufficient evidence to recommend for or against routine screening for HCV infection in adults at high risk for infection. I recommendation.

The USPSTF found no evidence that screening for HCV infection in adults at high risk (see Clinical Considerations) *leads to improved long-term health outcomes, although the yield of screening would be substantially higher in a high-risk population than in an average-risk population and there is good evidence that anti-viral therapy improves intermediate outcomes, such as viremia. There is, as yet, no evidence that newer treatment regimens for HCV infection, such as pegylated interferon plus ribavirin, improve long-term health outcomes. There is limited evidence from non-U.S. studies that older therapies have some long-term health benefits for patients referred for treatment, but the generalizability of these results to the U.S. population is unknown. Of those infected with HCV, the proportion who progress to liver disease is uncertain. There is limited evidence that 10% to 20% of patients with chronic HCV infection develop cirrhosis within 20 to 30 years after infection. There is also limited evidence that available treatments are effective in preventing cirrhosis in patients with asymptomatic HCV infection. Potential harms of screening and treatment include labeling, adverse treatment effects, and unnecessary biopsies, although there is limited evidence to determine the magnitude of these harms. As a result, the USPSTF could not determine the balance of benefits and harms of screening for HCV infection in adults at increased risk for infection.*

Clinical Considerations

- Established risk factors for HCV infection include current or past intravenous drug use, transfusion before 1990, dialysis, and being a child of an HCV-infected mother. Surrogate markers, such as high-risk sexual behavior (particularly sex with someone infected with HCV) and the use of illegal drugs, such as cocaine or marijuana, have also been associated with increased risk for HCV infection. The proportion of people who received blood or blood product transfusions before 1990 will continue to decline, and HCV infection will be associated mainly with intravenous drug use and, to some extent, unsafe sexual behaviors.

- Initial testing for HCV infection is typically done by enzyme immunoassay (EIA). In a population with a low prevalence of HCV infection (eg, 2%), approximately 59% of all

positive tests using the third-generation EIA test with 97% specificity would be false positive. As a result, confirmatory testing is recommended with the strip recombinant immunoblot assay (third-generation RIBA).

- Important predictors of progressive HCV infection include older age at acquisition; longer duration of infection; and presence of comorbid conditions, such as alcohol misuse, HIV infection, or other chronic liver disease. Asymptomatic individuals with HCV infection identified through screening may benefit from interventions designed to reduce liver injury from other causes, such as counseling to avoid alcohol misuse and immunization against hepatitis A and hepatitis B. However, there is limited evidence of the effectiveness of these interventions.

Discussion

HCV infection is the most common bloodborne pathogen in the United States.[3] Eight thousand to 10,000 deaths are associated with HCV infection annually.[3,4,5] The yearly incidence of HCV infection during the 1980s was estimated to be 230,000 cases per year and has declined to 25,000 cases in 2001 with the advent of measures to screen blood products for HCV infection.[1] HCV infection-related end-stage liver disease accounts for more than 30% of adult liver transplantation. HCV infection is acquired primarily by large or repeated percutaneous exposure to blood. The natural course of chronic HCV infection varies widely. A proportion of patients with chronic HCV infection may have only mild liver disease even after decades of infection or may never develop histologic evidence of liver disease.[6] The National Health and Nutrition Epidemiologic Survey-III (NHANES-III), conducted from 1988 through 1994, found a prevalence of 2.3% of anti-HCV antibody in adults older than 20 in the U.S. population.[7] The National Hepatitis Screening Survey found that intravenous drug use was the strongest risk factor for HCV infection (adjusted odds ratio [OR], 23), followed by hemodialysis, sex with an intravenous drug user, a history of blood transfusion, and male gender.[8] In cross-sectional studies of intravenous drug users, 65% of those who reported injecting drugs for 1 year or less and 50% to 90% of all intravenous drug users are infected with HCV.[9-14]

The USPSTF conducted a systematic review of the evidence on the effectiveness of screening tests and interventions aimed at improving intermediate and long-term health outcomes for HCV-infected adults. The review evaluated the magnitude of benefit of screening adults at average risk

and those at high risk for HCV infection. Enzyme immunoassay (EIA) is the initial screening test for anti-HCV antibodies. Polymerase Chain Reaction (PCR) is considered the gold standard in HCV-infection testing, as it is the only blood test for active infection. In 4 studies reviewed, third-generation EIA had a sensitivity ranging from 94% to 100% when compared with PCR or RIBA. One good quality study found EIA specificity to be 97% using PCR as the reference standard.[15] In populations with a low prevalence of HCV infection (2%), approximately 59% of all positive tests using the third-generation EIA test with 97% specificity would be false-positive tests.[16] Since the prevalence of HCV infection in high-risk groups is 50% to 90%, the yield of screening in individuals at increased risk would be substantially higher. The RIBA has 100% sensitivity when compared with EIA, but is a more expensive test. In 2 other studies, RIBA was found to have a sensitivity of 80% and 100%, respectively, compared with PCR.[1]

Because screening detects the presence of anti-HCV antibodies but does not discriminate between persistent and resolved infection, medical evaluation to determine the need for treatment of HCV infection includes PCR for viremia along with transaminase levels and liver biopsy. Pretreatment liver biopsy is currently recommended by the National Institutes of Health (NIH).[17-19]

To determine the magnitude of benefit of screening average- and high-risk adults for HCV infection, the USPSTF evaluated the evidence for the prevalence of HCV infection in these populations, the effectiveness of screening tests, the rate of disease progression, and the effectiveness of interventions in preventing disease progression. The prevalence estimates of HCV infection in average-risk groups and high-risk groups, such as intravenous drug users, vary significantly: 2.3% for those at average risk and 50% to 90% for those at high risk. No studies have evaluated the rate of disease progression in asymptomatic patients.

Potential harms from screening include effects of both false-positive and true-positive tests, which may lead to anxiety, effects on partner relationships, unnecessary liver biopsies, and treatment regimens that have a high incidence of adverse effects. Although false-positive tests do occur, they are uncommon if proper confirmatory tests are performed.[16] The harmful effects of true-positive results include anxiety and interventions in patients who would not have progressed to chronic liver disease.[2] The majority of patients receiving interferon-based therapies alone or in conjunction with ribavirin experience adverse effects. Patient withdrawal due to adverse effects from interferon monotherapy averaged 5%, and patient withdrawal from combination therapy

ranged from 10% to 20%.[2] The most common adverse event was flu-like syndrome, including myalgia, fatigue, headache, and fever.

Based on several cohort studies, cirrhosis develops in 10% to 20% of persons with chronic hepatitis C over a period of 20 to 30 years. Among those who are referred for treatment of HCV infection, only 30% to 40% were eligible for therapy and received treatment. Results from 3 well-conducted randomized controlled trials (RCTs) show that combination anti-viral therapy with pegylated interferon and ribavirin is effective in achieving a sustained virologic response, which is an intermediate health outcome, in 54% to 60% of patients 6 to 12 months after treatment.[2] Systematic reviews indicate lower efficacy (33%-41%) of non-pegylated interferon with ribavirin.[2] Because treatment of HCV infection is a relatively recent development, there is limited evidence of the long-term effectiveness of anti-viral therapy, especially combination therapy, on outcomes such as morbidity or mortality from chronic liver disease. Results from some studies, mostly international, suggest that patients treated with interferon have lower rates of hepatocellular cancer and lower mortality than untreated patients, but this association could reflect other differences between treated and untreated patients.[2] The extent to which these results are generalizable to the U.S. population is uncertain. There are limited data to determine the benefit of other interventions in infected patients, including immunization against hepatitis A and B and counseling to reduce damage from alcoholism and to decrease the probability of transmission.[2]

Currently, there is little evidence to determine which patients are likely to benefit from screening and current treatment regimens. Because the prevalence of HCV infection and rate of disease progression is low in adults at average risk, the harms of HCV-infection screening outweigh the benefits in this population. Those at high risk for HCV infection are also at increased risk for progression to cirrhosis and would be more likely to benefit from HCV-infection therapy. Although there is good evidence that anti-viral therapy improves intermediate outcomes, there is, as yet, no evidence that newer treatment regimens for HCV infection (pegylated interferon plus ribavirin) improve long-term health outcomes. As a result, the magnitude of the net benefit of screening high-risk adults for HCV infection is unknown.

Important gaps remain in the information needed to determine the benefits of hepatitis C screening. Because of the variability in the progression of HCV infection, it would be useful to define more precisely the rate of progression to clinically important liver disease among patients

detected by screening and to identify those who would most likely benefit from therapy. Studies are also needed to evaluate the effect of diagnosis and treatment on the quality of life. Studies are needed on the benefit of other interventions, such as counseling to prevent alcohol misuse and vaccinations for hepatitis A and hepatitis B, in HCV-infected individuals. Studies of risk factor assessment are needed to guide selective screening strategies. Since liver biopsy is part of the current workup for HCV infection and is a potentially harmful invasive procedure, studies to evaluate outcomes of patients who do not undergo biopsy would help to determine whether all or only selected patients should undergo this procedure.

Recommendations of Others

Recommendations for HCV-infection screening from other major entities can be obtained from the National Institutes of Health (NIH) Consensus Panel (2002) [17] at http://consensus.nih.gov/cons/116/091202116cdc_statement.htm and from the Centers for Disease Control and Prevention (CDC)[16] at ftp://ftp.cdc.gov/pub/Publications/mmwr/rr/rr4719.pdf. Both recommend screening for groups at high risk for HCV infection, although the way they define high-risk groups differs slightly. Both recommend screening for users of injection drugs, hemodialysis patients, and recipients of transfusions or organs (CDC recommendations cover the years before 1992, and NIH recommendations cover the years before 1990). In addition, the NIH panel recommends screening for individuals with multiple sexual partners, spouses or household contacts of HCV-infected patients, and those who share instruments for intranasal cocaine use; the CDC recommends screening for children born to mothers infected with HCV, those who received clotting factor concentrates before 1987, those with occupational exposure to HCV-positive blood, and patients with persistently abnormal alanine aminotransferase levels. Other groups identified by the CDC for whom routine screening is uncertain include recipients of transplanted tissue, those who use intranasal cocaine and other noninjecting illegal drugs, persons with a history of tattooing or body piercing, those with a history of multiple sex partners or sexually transmitted diseases, and long-term steady partners of HCV-positive persons. The CDC guidelines for reporting HCV test results can be accessed at http://www.cdc.gov/mmwr/PDF/rr/rr5203.pdf.

References

1. Chou R. Screening for Hepatitis C Virus Infection: Systematic Evidence Review No. 24. (Prepared by the Oregon Evidence-based Practice Center, Oregon Health & Science University under Contract No. 290-97-0018). Rockville, MD. Agency for Healthcare Research and Quality. March 2004. (Available on the AHRQ Website at: www.ahrq.gov/clinic/serfiles.htm.)

2. Chou R, Clark EC, Helfand MH. Screening for hepatitis C virus infection: a review of the evidence for the U.S. Preventive Services Task Force. *Ann Intern Med. 2004;140:465-479.*

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

4. Busch MP. Insights into the epidemiology, natural history and pathogenesis of hepatitis C virus infection from studies of infected donors and blood product recipients. *Transfus Clin Biol.* 2001;8:(3):200-206.

5. Kim WR. The burden of hepatitis C in the United States. *Hepatology.* 2002;36:S30-S34.

6. Schreiber GB, Busch MP, Kleinman SH, Korelitz JJ. The risk of transfusion-transmitted viral infections. The Retrovirus Epidemiology Donor Study. *N Engl J Med.* 1996;334(26):1685-1690.

7. Alter MJ, Kruszon-Moran D, Nainan OV, et al. The prevalence of hepatitis C virus infection in the United States, 1988 through 1994. *N Engl J Med.* 1999;341:(8):556-562.

8. Kaur S, Rybicki L, Bacon BR, et al. 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.

9. Garfein RS, Vlahov D, Galai N, et al. Viral infection in short-term injection drug users: the prevalence of the hepatitis C, hepatitis B, human immunodeficiency, and human t-lymphotropic viruses. *Am J Public Health.* 1996;86:655-661.

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

11. Patrick DM, Tyndall MW, Cornelisse PG, et al. Incidence of hepatitis C virus infection among injection drug users during an outbreak of HIV infection. *Can Med Assoc J.* 2001;165:(7):889-895.

12. Villano SA, Vlahov D, Nelson KE, et al. Incidence and risk factors for hepatitis C among injection drug users in Baltimore, Maryland. *J Clin Microbiol.* 1997;35:(12):3274-3277.

13. Bell J, Batey RG, Farrell GC, et al. Hepatitis C virus in intravenous drug users. *Med J Aust.* 1990;153:(5):274-276.

14. 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.

15. 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.

16. Alter MJ, Kuhnert WL, Finelli L. Guidelines for laboratory testing and result reporting of antibody to hepatitis C virus. Centers for Disease Control and Prevention. *MMWR.* 2003;52:(RR-3):1-16.

17. Management of hepatitis C: 2002. NIH Consens Statement 2002. 2003;19(3):1-46.

18. Dienstag JL. The role of liver biopsy in chronic hepatitis C. *Hepatology.* 2002;36:S152-S160.

19. Perrillo RP. The role of liver biopsy in hepatitis C. *Hepatology.* 1997;26:(Suppl 1):57S-61S.

APPENDIX A

U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS AND RATINGS

The Task Force grades its recommendations according to one of 5 classifications (A, B, C, D, I) reflecting the strength of evidence and magnitude of net benefit (benefits minus harms):

A. The USPSTF strongly recommends that clinicians provide [the service] to eligible patients. *The USPSTF found good evidence that [the service] improves important health outcomes and concludes that benefits substantially outweigh harms.*

B. The USPSTF recommends that clinicians provide [the service] to eligible patients. *The USPSTF found at least fair evidence that [the service] improves important health outcomes and concludes that benefits outweigh harms.*

C. The USPSTF makes no recommendation for or against routine provision of [the service]. *The USPSTF found at least fair evidence that [the service] can improve health outcomes but concludes that the balance of benefits and harms is too close to justify a general recommendation.*

D. The USPSTF recommends against routinely providing [the service] to asymptomatic patients. *The USPSTF found at least fair evidence that [the service] is ineffective or that harms outweigh benefits.*

I. The USPSTF concludes that the evidence is insufficient to recommend for or against routinely providing [the service]. *Evidence that [the service] is effective is lacking, of poor quality, or conflicting and the balance of benefits and harms cannot be determined.*

APPENDIX B

U.S. PREVENTIVE SERVICES TASK FORCE
STRENGTH OF OVERALL EVIDENCE

The USPSTF grades the quality of the overall evidence for a service on a 3-point scale (good, fair, poor):

Good: Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes.

Fair: Evidence is sufficient to determine effects on health outcomes, but the strength of the evidence is limited by the number, quality, or consistency of the individual studies, generalizability to routine practice, or indirect nature of the evidence on health outcomes.

Poor: Evidence is insufficient to assess the effects on health outcomes because of limited number or power of studies, important flaws in their design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes.