JAMA Clinical Guidelines Synopsis

Screening for Hepatitis C

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GUIDELINE TITLE Screening for Hepatitis C Virus Infection in Adults: US Preventive Services Task Force Recommendation Statement

DEVELOPER US Preventive Services Task Force (USPSTF)

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PRIOR VERSION March 2004

FUNDING SOURCE Agency for Healthcare Research and Quality (AHRQ)

TARGET POPULATION Asymptomatic adults without known liver disease or functional abnormalities

MAJOR RECOMMENDATIONS Screen all persons at high risk of hepatitis C virus (HCV) infection and offer one-time HCV screening to all adults born between 1945 and 1965 (B recommendation)

Summary of the Clinical Problem

Hepatitis C virus affects an estimated 180 million people worldwide, making it the most common chronic blood-borne pathogen.[1] Less than half of infected individuals clear their infection without treatment, and 15% to 40% of patients with HCV progress to cirrhosis or hepatocellular cancer. Hepatitis C virus infection is the most common indication for liver transplantation and is the cause of 8000 to 13 000 deaths in the United States each year.[2]

Since HCV testing of blood products was implemented in 1992, the 2 most important risk factors for HCV acquisition are past or current injection drug use and birth between 1945 and 1965.[3] Detection of HCV infection has proven difficult because behavioral risk histories are often incomplete, most newly infected individuals have no or mild nonspecific symptoms, and up to 50% of those infected have persistently normal serum transaminase values. Not surprisingly, 45% to 85% of all persons with chronic HCV infection are unaware that they are infected.[3] When patients are identified and receive proper HCV treatment, they can reduce their risk of hepatocellular cancer by 70% and all-cause mortality by 50%.[3]

Characteristics of the Guideline Source

These guidelines[2] were developed by the USPSTF, which is an independent volunteer panel of nonfederal experts in prevention and evidence-based medicine (**Table**). The task force is composed of primary care clinicians and experts in methods and health behavior. The guidelines were developed in coordination with a systematic review sponsored by the AHRQ. A draft of the recommendations was posted for public comment on the USPSTF website. A conflict of interest disclosure was completed by task force members prior to each meeting to provide information to AHRQ on potential financial, business/professional, and intellectual conflicts of interest.

Evidence Base

AHRQ commissioned 2 systematic reviews with a focus on screening and treatment to update its 2004 guidelines.[4,5] Both reviews focused on prior evidence gaps and new studies published since 2004. The screening review included 182 studies but found poor evidence of clinical benefit when screening was performed in the general US adult population, which has an estimated HCV prevalence of 1% to 1.5%.[4] In contrast, retrospective studies that focused on populations with multiple risk factors found sensitivities greater than 90% and a favorable number needed to screen of fewer than 20.

Strategies specifically targeted toward individuals with a history of intravenous drug use were associated with much higher specificity but missed up to two-thirds of all infected persons. This led to a pragmatic recommendation to screen baby boomers, those born between 1945 and 1965, a cohort with 3 times the HCV antibody prevalence of that in the general adult population and estimated to contain 76% of all US individuals infected with HCV.[4] This targeted screening was supported by a large cost-effectiveness analysis that found large estimated reductions in HCV-related mortality with screening based on birth year vs risk-based screening alone.[6]

Because a complete assessment of the harms and benefits of screening could not be made without consideration of the effectiveness of antiviral treatments, AHRQ performed a complementary review of antiviral treatments.[5] Recognizing that newer therapies are emerging, the authors assessed 90 randomized trials and observational studies examining current antiviral regimens and found substantially higher sustained viral response rates in patients with HCV genotype 1 who received triple antiviral therapy (pegylated interferon, ribavirin, and boceprevir or teleprevir) vs those who received dual therapy (pegylated interferon and ribavirin).

Benefits and Harms

The USPSTF review on screening considered evidence on the diagnostic accuracy of the various noninvasive confirmatory tests to di-

Table. Guideline Rating

Rating Standard	Rating
1. Establishing transparency	Good
2. Management of conflict of interest in the guideline development group	Good
3. Guideline development group composition	Fair
4. Clinic practice guideline–systematic review intersection	Good
5. Establishing evidence foundations and rating strength for each of the guideline recommendations	Good
6. Articulation of recommendations	Good
7. External review	Good
8. Updating	Good
9. Implementation issues	Fair

agnose fibrosis or cirrhosis compared with liver biopsy as the reference standard. Several tests were found to have good to very good diagnostic accuracy, with area under the receiver operating curve values of 0.75 to 0.86 for fibrosis and 0.80 to 0.91 for cirrhosis, respectively.[4] One retrospective study found no difference in sustained viral response rates between patients who did not have a biopsy prior to treatment and patients who did have a biopsy (41% vs 44%; $P = .87$).[7] Given the accuracy of noninvasive screening tests and the increasing availability of effective treatments for HCV, the USPSTF concluded that screening high-risk populations and those born between 1945 and 1965 was of moderate benefit.

The review found little evidence on the harms of screening, but potential harms were noted to include anxiety, patient labeling, and feelings of stigmatization. Although harms with liver biopsy were noted (eg, bleeding, infection, pain), the use of biopsy to guide treatment decisions is declining as noninvasive testing has proven its ability to accurately diagnose fibrosis and cirrhosis.

Traditional interferon-based antiviral therapy was found to have high rates of harm, commonly noted by fatigue, headache, flulike symptoms, hematologic conditions, and rash. Although it was noted that treatment regimens are given only for short periods (4 to 48 weeks, depending on virologic response and genotype), symptoms usually resolve following treatment cessation, and serious events are highly uncommon. The emergence of generally shorter-duration, increasingly effective oral therapies (which do not require interferon) has likely improved the ratio of benefit to harm.

Discussion

The 2004 USPSTF guidelines recommended against screening for HCV in adults not at increased risk of infection (D recommendation) and found insufficient evidence to recommend for or against screening in high-risk populations (I statement). The recent screening recommendations (B recommendation) are the result of increasing awareness of HCV as a public health concern in conjunction with the improved outcomes, shorter durations of therapy, and reduced toxicity associated with advances in antiviral therapy. In 2010, the Institute of Medicine identified hepatitis as an "underappreciated health concern" and provided recommendations to improve prevention and control. In 2011, the US Department of Health and Human Services announced an explicit goal of increasing awareness of infection in those living with HCV.

To achieve this goal, comprehensive screening strategies need to be implemented, a challenge because clinician knowledge of disease prevalence, natural history, and follow-up testing procedures is low, with a 2012 study reporting that only 59% of physicians regularly screen for patient risk factors, and only half of patients found to have HCV are referred to a subspecialist for further care.[8]

The 2013 USPSTF updated guidelines, in conjunction with those issued by the Centers for Disease Control and Prevention in 2012[9] and the 2014 guidelines released by the American Association for the Study of Liver Diseases in conjunction with the Infectious Diseases Society of America, reflect increasing evidence on the benefits of age-based HCV testing and stress the need for linkage to treatment to improve health outcomes. In contrast, the 2013 World Health Organization guidelines did not make a specific birth cohort screening recommendation but highlighted risk-based screening. With the release of directly acting oral antivirals such as simeprevir and sofosbuvir, the case for screening and referral has become even more persuasive.

Areas in Need of Future Study or Ongoing Research

Further research in effective screening guideline implementation is required, particularly on frequency of testing in defined high-risk populations such as people who inject drugs and for one-time screening in low-risk individuals born between 1945 and 1965.

Moreover, modeling studies suggest that imperfect follow-up of positive screening results, leading to poor linkage to therapy, may reduce the real-world effectiveness of HCV therapies by approximately 75%,[8] highlighting the importance for researchers to track successful completion of therapy, not simply initial screening and referral rates. The cost of the new oral agents is an important potential barrier, especially for low-income populations, and longer experience with their adverse effects will help define their place in care.

Related guidelines and other resources

World Health Organization
http://www.who.int/hiv/pub/hepatitis/hepatitis-c-guidelines/en/

American Association for the Study of Liver Diseases/Infectious Diseases Society of America
http://www.hcvguidelines.org/node/69

Kohli A, Shaffer A, Sherman A, Kottilil S. Treatment of hepatitis C: a systematic review. *JAMA*. 2014;312(6):631-640.

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