Screening for Hepatitis C Virus Infection in Adults

Executive Summary

Background

Hepatitis C virus (HCV) is a single-stranded, positive-sense RNA virus of the family Flaviviridae. HCV is the most common chronic bloodborne pathogen in the United States. The prevalence of anti-HCV antibody in the United States is estimated at 1.6 percent. Approximately 78 percent of those who test positive for anti-HCV antibody have the HCV detectable in the blood (viremia), indicating chronic infection; those with anti-HCV antibody but no viremia are considered to have cleared the infection. About two-thirds of patients with HCV infection were born between 1945 and 1964, with the highest prevalence (4.3 percent) in people 40 to 49 years of age in 1999–2002. The prevalence of chronic HCV infection is thought to have peaked in 2001 at 3.6 million people. The yearly incidence of HCV infection averaged more than 200,000 cases per year in the 1980s, but by 2001 had declined to around 25,000 cases per year. The Centers for Disease Control and Prevention (CDC) estimated 16,000 new cases of HCV infection in 2009. HCV infection is a leading cause of complications from chronic liver disease and was associated with an estimated 15,000 deaths in the United States in 2007. One study estimated that the total number of patients with cirrhosis will peak at 1.0 million in 2020, though rates of hepatic decompensation and liver cancer are expected to continue to rise for another

Effective Health Care Program

The Effective Health Care Program was initiated in 2005 to provide valid evidence about the comparative effectiveness of different medical interventions. The object is to help consumers, health care providers, and others in making informed choices among treatment alternatives. Through its Comparative Effectiveness Reviews, the program supports systematic appraisals of existing scientific evidence regarding treatments for high-priority health conditions. It also promotes and generates new scientific evidence by identifying gaps in existing scientific evidence and supporting new research. The program puts special emphasis on translating findings into a variety of useful formats for different stakeholders, including consumers. The full report and this summary are available at www.effectivehealthcare.ahrq.gov/reports/final.cfm.
10 to 13 years given the long lag time between infection and development of cirrhosis and other complications.2 HCV-related end-stage liver disease is the most common indication for liver transplantation among American adults, accounting for more than 30 percent of cases, with a fivefold increase in the number of patients with HCV who underwent liver transplantation between 1990 and 2000.5,6 Studies suggest that about half of the recently observed threefold increase in incidence of hepatocellular carcinoma is related to acquisition of HCV infection two to four decades earlier.8,9 HCV without cirrhosis is associated with worse quality of life measures and symptoms (primarily fatigue) compared with the general population.10-14

HCV is primarily acquired via percutaneous exposures to infected blood. The strongest risk factor for HCV infection is injection drug use. The prevalence of HCV infection in injection drug users varies widely depending on age, duration of injection drug use, and other factors (such as availability and use of needle exchange programs).15 Prevalences range from less than 50 percent in more recent studies of younger injection drug users to more than 90 percent in older studies of older injection drug users.16-22 About 60 percent of new infections occur in individuals who report injecting drugs within the last 6 months.3 Although large population-based studies16,17,23 report independent associations between HCV infection and some high-risk sexual behaviors (multiple sexual partners, unprotected sex, and/or sex with a person infected with HCV infection or using injection drugs), the efficiency of transmission via sexual contact appears to be low, and high-risk sexual behaviors may be a marker for unacknowledged drug use or other risk factors. Transfusions prior to 1992 are a risk factor for HCV infection but transfusions after 1992 are not an important source of infection due to the implementation of effective screening programs for donated blood.24,25

The natural course of chronic HCV infection varies. Many patients with chronic HCV infection have only mild liver disease even after decades of infection or never develop histologic evidence of liver disease.26 In other patients, inflammation and fibrosis of the liver may progress to cirrhosis, which can lead to end-stage liver disease or hepatocellular carcinoma. Once cirrhosis develops, patients have a much higher risk of death, and some may benefit from liver transplantation. Well-established predictors of advanced fibrosis in those with chronic HCV infection include older age at infection, longer duration of infection, male sex, concomitant HIV or hepatitis B virus (HBV) infection, and greater alcohol use.26-28 Other factors that may be associated with increased risk of fibrosis include insulin resistance, hepatic steatosis, higher viral load, and the presence of certain HLA class II polymorphisms.

Estimating the proportion of patients in the general population with HCV infection who progress to cirrhosis is difficult because the time of acquisition is often unclear and important endpoints often do not occur until after decades of infection.29 For example, six retrospective cohort studies of HCV-infected adults with known time of infection (based on an identified exposure, often to contaminated blood products during young adulthood) reported cirrhosis in 0 to 10 percent of patients after at least 10 years of followup.14,30-35 Overall, studies of community cohorts estimate cirrhosis in an average of 7 percent of people after 20 years of HCV infection, with rates about twice as high in clinical and referral cohorts.28,36 Studies with longer followup suggest that progression to cirrhosis may accelerate after 20 years of chronic infection.33

Screening for HCV infection in asymptomatic adults who have no history of liver disease or known liver enzyme abnormalities may identify infected patients at earlier stages of disease, before they develop serious or irreversible liver damage. A high proportion of people with chronic HCV infection are thought to be unaware of their status. One study of young injection drug users in the United States found that 72 percent were unaware of their HCV-positive status.37 Patients with chronic HCV infection may be eligible for antiviral treatments, which have become increasingly effective at long-term eradication of HCV in the blood. In addition, identification of HCV infection might help prevent transmission by decreasing high-risk injection drug use and other risky behaviors, or identify those who might benefit from hepatitis A or B vaccinations, alcohol cessation counseling, or other interventions.

Screening for HCV infection in asymptomatic individuals without known liver enzyme abnormalities might identify patients who could benefit from such interventions. Recommendations on HCV screening vary. In 2004, the United States Preventive Services Task Force (USPSTF) recommended against screening for HCV infection in adults not at increased risk (D recommendation) and found insufficient evidence to recommend for or against screening in adults at high-risk (I recommendation).38 The 2004 evidence review commissioned by the USPSTF to inform its recommendations found that screening is accurate in identifying people with HCV infection and that antiviral treatments improved intermediate outcomes such as viremia.39 The D recommendation in low-risk
individuals was based on evidence indicating a relatively low prevalence of HCV infection, natural history studies showing that most patients with chronic HCV infection do not develop major long-term negative health outcomes (such as death, cirrhosis, or need for liver transplantation), lack of direct evidence showing that screening or antiviral treatments improves important health outcomes, and potential harms of screening including those related to unnecessary treatments and labeling. Although the USPSTF concluded that screening high-risk populations would be a more efficient strategy than screening average-risk populations, it found insufficient evidence on the effects of screening or antiviral treatments on health outcomes and on the association between improved intermediate and clinical outcomes to determine the balance of benefits and harms with screening. 

Unlike the USPSTF, other groups (including the American Association for the Study of Liver Disease, the Infectious Diseases Society of America, and the American College of Gastroenterology) recommend screening in higher risk patients. These recommendations are based on the higher prevalence of HCV infection in higher risk populations, acceptance of the link between improved intermediate outcomes following antiviral treatments and improved clinical outcomes, and presumed public health benefits related to the potential for reduced risky behaviors and transmission. The CDC recently recommended the screening of high-risk patients as well as age-cohort based HCV screening of all people born between 1945 and 1965.

Mother-to-child (vertical) transmission is believed to be the main route of HCV infection acquisition in children. Estimates of vertical transmission range from 3 to 10 percent. The risk of transmission is highest among women with a high viral load at the time of delivery and among women coinfected with HIV. Routine prenatal screening for HCV infection is not currently recommended; the CDC and the 2007 American College of Obstetricians and Gynecologists recommend offering HCV screening to at-risk pregnant women and the 2004 USPSTF recommendations did not address screening for HCV during pregnancy. While antiviral therapies are contraindicated in pregnancy due to teratogenic risks, identification of HCV infection during pregnancy could facilitate decisionmaking around the management and use of interventions during labor and delivery or in the perinatal period that might reduce risk of mother-to-child transmission.

The purpose of this report is to review the evidence on screening for chronic HCV infection in asymptomatic adults without known liver enzyme abnormalities. The Agency for Healthcare Research and Quality (AHRQ), which commissioned this review, also commissioned a separate but complementary review on effectiveness of antiviral treatments. Together, these reviews will be used by the USPSTF to update its recommendations on HCV screening. This review focuses on research gaps identified in the 2004 USPSTF review and new studies published since that review. In addition, it evaluates evidence on screening for both pregnant and nonpregnant adults.

Objectives

The following Key Questions are the focus of our report:

Key Question 1

a. Does screening for HCV infection in nonpregnant adults without known abnormal liver enzymes reduce mortality and morbidity due to HCV infection, affect quality of life, or reduce incidence of HCV infection?

b. Does screening for HCV infection during pregnancy reduce vertical transmission of HCV or improve mortality or morbidity for the mother or child?

Key Question 2

a. What is the effectiveness of different risk- or prevalence-based methods for screening for HCV infection on clinical outcomes?

b. What is the sensitivity and number needed to screen to identify one case of HCV infection of different risk- or prevalence-based methods for screening for HCV infection?

Key Question 3

What are the harms associated with screening for HCV infection, including adverse effects such as anxiety, labeling, and impact on relationships?

Key Question 4

a. What is the comparative effectiveness and comparative diagnostic accuracy of various tests and strategies for the workup to guide treatment decisions in patients who are HCV positive?

b. What proportion of patients with screen-detected HCV infection receives treatment?

Key Question 5

What are the harms associated with the workup for guiding treatment decisions?
Key Question 6

a. How effective is counseling or immunizations of patients with HCV infection at improving health outcomes or reducing the spread of HCV?

b. Does becoming aware of positive HCV infection status decrease high-risk behaviors?

c. How effective is counseling or immunization of patients with HCV infection at improving intermediate outcomes, including change in high-risk behaviors?

Key Question 7

Do any interventions decrease or increase the vertical transmission of HCV during delivery or in the perinatal period?

Analytic Framework

The analytic framework (Figure A) depicts the Key Questions in the framework of the population, interventions, and outcomes considered in the review. The figure is a modified version of a larger framework depicting the effect of both screening and treatment for HCV in adults. This report focuses on the screening portion of the framework. The overarching Key Questions (1a and 1b) in the analytic framework address direct evidence that screening for HCV infection improves important health outcomes compared with not screening. When such direct evidence is sparse or unavailable, indirect evidence can be used to assess the effects of screening on health outcomes. Therefore, the remainder of the analytic framework evaluates the chain of indirect evidence needed to link screening for HCV infection with improvements in important health outcomes. Links in the chain of indirect evidence include the performance of the screening test or testing strategy for identifying individuals with HCV infection, the clinical utility and diagnostic accuracy of the workup used to guide treatment decisions, and the effectiveness of treatments in those identified as infected with HCV infection, as well as any harms from the screening test and subsequent diagnostic tests and treatments. We did not re-review the accuracy of HCV antibody testing, which the prior USPSTF review found to be highly accurate. The proportion of patients with HCV infection who receive antiviral treatment is important for understanding potential benefits of screening, as not all patients will receive (and potentially benefit from) treatment. Critical gaps in any of the links of the indirect chain of evidence can make it impossible to reliably estimate benefits and harms of screening.

The target population was adults (including pregnant women) without signs or symptoms of liver disease or known liver enzyme abnormalities. We excluded post-transplant patients, HIV patients, hemodialysis patients, and patients with occupational exposures. The interventions include screening for HCV infection risk factors, screening for HCV antibody, diagnostic tests for workup of treatable disease, interventions to prevent mother-to-child transmission of HCV infection, counseling against risky behaviors, and immunization for other hepatitis infections. In people with chronic HCV infection, becoming infected with hepatitis A or hepatitis B virus may result in fulminant hepatitis or more rapid progression of liver disease. Clinical outcomes were mortality, morbidity, quality of life, and HCV transmission, as well as harms of screening and/or workup; intermediate outcomes were risky behaviors (virologic and histologic intermediate outcomes were evaluated in a complementary review on antiviral treatments).

Methods

Input From Stakeholders

The topic of HCV screening was nominated for a comparative effectiveness review (CER) in a public process. The Key Questions were proposed in the public nomination process and developed by investigators from the Evidence-based Practice Center with input from expert Key Informants, who helped to refine Key Questions, identify important methodological and clinical issues, and define parameters for the review of evidence. The revised Key Questions were then posted to a public Web site for comment. AHRQ agreed upon the final Key Questions after reviewing the public comments and receiving additional input from a Technical Expert Panel (TEP) convened for this report. Prior to participation in this report, the TEP members disclosed all financial or other conflicts of interest. The AHRQ Task Order Officer and the authors reviewed all of these disclosures and determined the panel members had no significant conflicts of interest that precluded participation.

Data Sources and Selection

To identify articles relevant to each Key Question, a research librarian searched Ovid® MEDLINE, Embase, Scopus, and PsycINFO from 1947 to May 2012. Gray literature was identified by searching clinical trial registries (Ovid® EBM Reviews: Cochrane Central Register of Controlled Trials, ClinicalTrials.gov, Current Controlled
**Figure A. Analytic framework: Screening for hepatitis C virus infection in adults**

HCV = hepatitis C virus; QOL = quality of life; SVR = sustained virologic response

Note: Portions in light blue shading refer to Key Questions addressed in a separate review on antiviral treatments.33

aNonpregnant and pregnant adults without abnormal lab values. Excluding people with HIV, transplant recipients, and patients with renal failure.

bHCV antibody testing with confirmatory HCV RNA testing as indicated.

cInterventions that may affect vertical transmission of HCV, such as cesarean section, amniocentesis, fetal monitoring, or others.

dRefers to eligibility for antiviral treatment based on viral and host factors.

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1a, 1b, 2a

1. Hepatitis C Screening
   - Asymptomatic Adults
     - 2
     - HCV +
     - 4a, 4b
     - HCV −
     - 5
     - Ineligible
     - 6a, 7
     - Antiviral Treatment
       - SVR
       - Histologic changes
       - Reductions in high-risk behaviors
       - 6b, 6c
       - Eligible
       - 4a, 4b
       - Counseling
       - Pregnancy Interventions
       - Workup to Guide Treatment Decisions
       - 1a, 1b, 2a
       - Harms
       - 3

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Harmas point to Counseling, Pregnancy Interventions, Antiviral Treatment, and Harms.

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Trials, Clinical Trial Results, and WHO Trial Registries) and grants databases (NIHRePORTER, HSRProj, and AHRQ GOLD). We supplemented the electronic searches by reviewing the reference lists of retrieved articles. We updated searches prior to finalization of the report to identify new publications.

We developed criteria for inclusion and exclusion of studies based on the Key Questions and the populations, interventions, comparators, outcomes, timing, and setting (PICOTS) approach. Papers were selected for full review if they were about chronic HCV infection, were relevant to Key Questions in the analytic framework, and met the predefined inclusion criteria.

We restricted inclusion to English language articles and excluded studies only published as abstracts. Studies of nonhuman subjects were excluded, as were studies that did not include original data.

Abstracts and full-text articles were dually reviewed for inclusion or exclusion for each Key Question. Full-text articles were obtained for all studies that either investigator identified as potentially meeting inclusion criteria. Two investigators independently reviewed all full-text articles for final inclusion or exclusion. Discrepancies were resolved through discussion and consensus, and a third investigator was included in the discussion if necessary.

We included randomized trials, cohort studies, and case-control studies pertinent to all Key Questions. We also included studies that reported the diagnostic accuracy of noninvasive tests for evaluating fibrosis or cirrhosis in patients with chronic HCV infection compared with liver biopsy.

Data Extraction and Quality Assessment

We extracted the following data from included trials: study design, setting, population characteristics (including sex, age, ethnicity/race, and diagnosis), eligibility and exclusion criteria, hepatitis C intervention and comparisons, the method of outcome ascertainment if available, and results for each outcome. Evidence tables with included studies are presented for all Key Questions unless there was only very weak evidence (i.e., because of major methodological shortcomings or studies designed without comparison groups).

For studies reporting the diagnostic yield of different screening strategies, we computed the number needed to screen to identify one case of HCV infection by dividing the number of screening tests performed by the number of HCV cases identified. The proportion screened was the number of patients screened upon application of a particular screening strategy, divided by the total number of patients assessed.

For studies of diagnostic accuracy, we created 2x2 tables from information provided (usually sample size, prevalence, sensitivity, and specificity) and compared calculated measures of diagnostic accuracy based on the 2x2 tables with reported results. Although we abstracted data for severe fibrosis (defined as biopsy showing META VIR F3-F4, Ishak 4-6, or equivalent), we summarized results for fibrosis (defined as biopsy showing META VIR F2-F4, Ishak 3-6, or equivalent) and cirrhosis (defined as biopsy showing META VIR F4, Ishak 5-6, or equivalent), unless there was insufficient evidence for fibrosis. We also abstracted reported area under the receiver operating characteristic curve (AUROC). The AUROC, which is based on sensitivities and specificities across a range of test results, is a measure of discrimination, or the ability of a test to distinguish people with a condition from people without. An AUROC of 1.0 indicates perfect discrimination and an AUROC of 0.5 indicates complete lack of discrimination. Interpretation of AUROC values between 0.5 and 1.0 is somewhat arbitrary, but a value of 0.90 to <1.0 may be classified as excellent, 0.80 to <0.90 good, 0.70 to <0.80 fair, and <0.70 poor. Data abstraction for each study was completed by two investigators: the first abstracted the data, and the second reviewed the abstracted data for accuracy and completeness.

We assessed the quality of each study based on predefined criteria. We adapted criteria from methods proposed by Downs and Black (observational studies), USPSTF, and the Quality Assessment of Diagnostic Accuracy Studies-2 Group. The criteria used are consistent with the approach recommended by AHRQ in the Methods Guide for Comparative Effectiveness Reviews. We used the term “quality” rather than the alternate term “risk of bias”, both refer to internal validity.

We rated the quality of each randomized trial based on the methods used for randomization, allocation concealment, and blinding; the similarity of compared groups at baseline; maintenance of comparable groups; adequate reporting of dropouts, attrition, crossover, adherence, and contamination; loss to followup; the use of intent-to-treat analysis; and ascertainment of outcomes.

We rated the quality of each cohort study based on whether it used nonbiased selection methods to create an inception cohort; whether it evaluated comparable groups; whether rates of loss to followup were reported and acceptable; whether it used accurate methods for ascertaining...
We recorded factors important for understanding the applicability of studies, such as whether the publication adequately described the study population, how similar patients were to populations likely to be targeted by screening, whether differences in outcomes were clinically (as well as statistically) significant, and whether the interventions and tests evaluated were reasonably representative of standard practice. We also recorded the funding source and role of the sponsor. We did not assign a rating of applicability (such as “high” or “low”) because applicability may differ based on the user of this report.

We did not attempt to pool studies of screening or treatments quantitatively due to small numbers of studies, lack of randomized trials, and substantial clinical diversity with respect to the populations, settings, and comparisons evaluated. We also did not quantitatively pool results on diagnostic accuracy (such as creating a summary receiver operating characteristic curve) due to differences across studies in populations evaluated, differences in how fibrosis or cirrhosis were defined, and methodological limitations in the studies. Instead, we created descriptive statistics with the median sensitivity and specificity at specific cutoffs and reported AUROCs, along with associated ranges. The total range, rather than the interquartile range, was chosen because certain outcomes were only reported by a few studies and the summary range highlighted the greater variability (and uncertainty) in the estimates.

We rated the strength of evidence for each Key Question using the four categories recommended in the AHRQ Methods Guide. We synthesized the overall quality of each body of evidence, based on the type and quality of studies (graded good, fair, or poor); the precision of the estimate of effect, based on the number and size of studies and confidence intervals for the estimates (graded high, moderate, or low); the consistency of results between studies (graded high, moderate, or low); and the directness of the evidence linking the intervention and health outcomes (graded direct or indirect). We were not able to assess for publication bias in studies of interventions using graphical or statistical methods due to small number of studies, methodological shortcomings, differences across studies in designs, measured outcomes, and other factors. Rather, we searched clinical trial registries and grants databases in order to identify relevant unpublished studies and qualitatively assess their potential effects on conclusions. We rated the strength of evidence for each comparison and outcome using the four categories recommended in the AHRQ guide. A “high” grade indicates high confidence that the evidence reflects the true
effect and that further research is very unlikely to change our confidence in the estimate of effect. A “moderate” grade indicates moderate confidence that the evidence reflects the true effect and further research may change our confidence in the estimate of effect and may change the estimate. A “low” grade indicates low confidence that the evidence reflects the true effect and further research is likely to change the confidence in the estimate of effect and is likely to change the estimate. An “insufficient” grade indicates evidence either is unavailable or too limited to permit a conclusion.

Peer Review

Experts in gastroenterology, hepatology, and infectious disease fields and individuals representing stakeholder and user communities were invited to provide external peer review of this CER; AHRQ and an associate editor also provided comments. The draft report was posted on the AHRQ Web site for 4 weeks to elicit public comment. We addressed all reviewer comments, revising the text as appropriate, and documented comments and responses in a disposition report that will be made available 3 months after AHRQ posts the final CER on its Web site.

Results

The strength of the evidence and key findings of this review are summarized in Table A. Of the 10,786 citations identified at the title and abstract level, we screened and reviewed 808 full-length articles. A total of 182 studies were included. We identified no relevant unpublished studies from searches on clinical trials registries and grants databases. There was no direct evidence on clinical benefits associated with screening compared with no screening (or of different screening approaches) in nonpregnant or pregnant adults. Retrospective studies found that screening strategies targeting multiple risk factors were associated with sensitivities of over 90 percent and numbers needed to screen to identify one case of HCV infection of less than 20. More narrowly targeted alternative screening strategies (such as only screening persons with a history of injection drug use) were associated with numbers needed to screen of less than two, but missed up to two-thirds of infected patients. Data on harms of screening (such as labeling and anxiety) were sparse. A number of indices based on panels of blood tests were associated with an AUROC of 0.75 to 0.86 for diagnosing fibrosis and an AUROC of 0.80 to 0.91 for diagnosing cirrhosis compared with liver biopsy, but there was insufficient evidence to determine clinical outcomes associated with different strategies for evaluating patients with HCV infection. Limited evidence suggested that knowledge of HCV status and counseling interventions may reduce alcohol use and risky injection drug use behaviors, but more evidence is needed to demonstrate long-term sustainability and effects on clinical outcomes and transmission risk. In pregnant women, cohort studies found no clear association between mode of delivery and risk of vertical transmission of HCV infection and consistently found no association between breastfeeding and transmission risk. Evidence on the association between other labor and delivery management practices and risk of vertical transmission of HCV infection was sparse, but suggested that prolonged rupture of membranes is associated with increased risk.

Table A. Summary of evidence on comparative benefits and harms of screening for hepatitis C virus infection

<table>
<thead>
<tr>
<th>Key Question</th>
<th>Strength of Evidence</th>
<th>Summary</th>
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<tbody>
<tr>
<td>Key Question 1a. Does screening for HCV infection in nonpregnant adults without known abnormal liver enzymes reduce mortality and morbidity due to HCV infection, affect quality of life, or reduce incidence of HCV infection?</td>
<td>Insufficient</td>
<td>No studies.</td>
</tr>
<tr>
<td>Key Question 1b. Does screening for HCV infection during pregnancy reduce vertical transmission of HCV or improve mortality or morbidity for the mother or child?</td>
<td>Insufficient</td>
<td>No studies.</td>
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</table>
## Table A. Summary of evidence on comparative benefits and harms of screening for hepatitis C virus infection (continued)

<table>
<thead>
<tr>
<th>Key Question</th>
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<tbody>
<tr>
<td>Key Question 2a. What is the effectiveness of different risk- or prevalence-based methods for screening for HCV infection on clinical outcomes?</td>
<td>Insufficient</td>
<td>No studies.</td>
</tr>
<tr>
<td>Key Question 2b. What is the sensitivity and number needed to screen to identify one case of HCV infection of different risk- or prevalence-based methods for screening for HCV infection?</td>
<td>Low</td>
<td>Five studies found that screening strategies targeting multiple risk factors were associated with sensitivities of over 90% and numbers needed to screen to identify one case of HCV infection of less than 20. More narrowly targeted screening strategies were associated with numbers needed to screen of less than two, but with the trade-off of missing up to two-thirds of infected patients. All studies were retrospective and had methodological shortcomings.</td>
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<tr>
<td>Key Question 3. What are the harms associated with screening for HCV infection, including adverse effects such as anxiety, labeling, and impact on relationships?</td>
<td>Insufficient</td>
<td>Five studies of patients diagnosed with HCV infection suggested potential negative psychological and social effects, but are difficult to interpret due to small sample sizes and methodological shortcomings, including no unscreened comparison group.</td>
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<tr>
<td>Key Question 4a. What is the comparative effectiveness and comparative diagnostic accuracy of various tests and strategies for the workup to guide treatment decisions in patients who are HCV positive?</td>
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<tr>
<td>Clinical Outcomes</td>
<td>Insufficient</td>
<td>One retrospective cohort study (n=156) of patients who received interferon plus ribavirin therapy found no difference in rates of sustained virologic rates between patients who did not undergo biopsy prior to treatment compared with matched patients who did undergo biopsy.</td>
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<tr>
<td>Diagnostic accuracy: Platelet counts vs. liver biopsy</td>
<td>Low</td>
<td>For fibrosis (defined as META VIR F2-F4, Ishak 3-6, or equivalent), the median AUROC was 0.71 (range 0.38 to 0.94) in 5 studies. For cirrhosis (defined as META VIR F4, Ishak 5-6, or equivalent), the AUROC was 0.89 (range 0.64 to 0.99) in 5 studies.</td>
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<tr>
<td>Diagnostic accuracy: Age-platelet index vs. liver biopsy</td>
<td>Moderate</td>
<td>For fibrosis, the median AUROC was 0.69 (range 0.64 to 0.77) in 4 studies. For cirrhosis, the median AUROC was 0.89 (range 0.67 to 0.91) in 4 studies.</td>
</tr>
<tr>
<td>Diagnostic accuracy: Aspartate aminotransferase-platelet ratio index (APRI) vs. liver biopsy</td>
<td>High</td>
<td>For fibrosis, the median AUROC was 0.76 (range 0.58 to 0.95) in 44 samples reported in 42 studies. For cirrhosis, the median AUROC was 0.85 (range 0.61 to 0.92) in 32 studies.</td>
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<tr>
<td>Diagnostic accuracy: Aspartate aminotransferase-alanine aminotransferase ratio (AST/ALT ratio, or AAR) vs. liver biopsy</td>
<td>High</td>
<td>For fibrosis, the median AUROC was 0.59 (range 0.50 to 0.82) in 9 studies. For cirrhosis, the median AUROC was 0.66 (range 0.52 to 0.91) in 11 studies.</td>
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<tr>
<td>Diagnostic accuracy: Cirrhosis Discriminant Score (CDS, also Bonacini Index) vs. liver biopsy</td>
<td>Moderate</td>
<td>For cirrhosis, the median AUROC was 0.77 (range 0.70 to 0.91) in 6 studies. Although the CDS was developed to identify cirrhosis, 3 studies reported a median AUROC of 0.67 (range of 0.64 to 0.71) for fibrosis.</td>
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<tr>
<td>Diagnostic accuracy: Enhanced Liver Fibrosis Index (ELF) or Simplified Enhanced Liver Fibrosis Index (Simplified ELF) vs. liver biopsy</td>
<td>Moderate</td>
<td>For fibrosis, the median AUROC was 0.81 (range 0.72 to 0.87) in 7 samples reported in 5 studies. For cirrhosis, the median AUROC was 0.88 (range 0.78 to 0.91) in 6 samples reported in 3 studies.</td>
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</table>
### Table A. Summary of evidence on comparative benefits and harms of screening for hepatitis C virus infection (continued)

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<tbody>
<tr>
<td><strong>Key Question 4a. What is the comparative effectiveness and comparative diagnostic accuracy of various tests and strategies for the workup to guide treatment decisions in patients who are HCV positive? (continued)</strong></td>
<td></td>
<td><strong>Diagnostic accuracy: FIB-4 vs. liver biopsy</strong> Moderate For severe fibrosis (defined as META VIR F3-F4, Ishak 4-6, or equivalent), the median AUROC was 0.86 (range 0.73 to 0.90) in 4 studies. For cirrhosis, the median AUROC was 0.87 (range 0.83 to 0.92) in 6 studies.</td>
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<tr>
<td><strong>Diagnostic accuracy: FibroIndex vs. liver biopsy</strong> Moderate For fibrosis, the median AUROC was 0.71 (range 0.58 to 0.86) in 5 samples reported in 4 studies. For cirrhosis, the AUROCs were 0.86 and 0.92 in 2 studies.</td>
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<td><strong>Diagnostic accuracy: Fibrometer vs. liver biopsy</strong> Moderate For fibrosis, the median AUROC was 0.82 (range 0.78 to 0.85) in 8 samples reported in 7 studies. For cirrhosis, the median AUROC was 0.91 (range 0.89 to 0.94) in 5 studies.</td>
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<td><strong>Diagnostic accuracy: FibroSpect II vs. liver biopsy</strong> Low For fibrosis, the median AUROC was 0.86 (range 0.82 to 0.90) in 4 studies. No study evaluated the diagnostic accuracy of FibroSpect II for cirrhosis.</td>
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<tr>
<td><strong>Diagnostic accuracy: Fibrotest vs. liver biopsy</strong> High For fibrosis, the median AUROC for was 0.79 (range 0.70 to 0.89) in 21 samples reported in 20 studies. For cirrhosis, the median AUROC was 0.86 (range 0.71 to 0.92) in 11 studies.</td>
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<td><strong>Diagnostic accuracy: Forns' Index vs. liver biopsy</strong> High For fibrosis, the median AUROC was 0.75 (range 0.60 to 0.86) in 16 samples reported in 15 studies. For cirrhosis, the median AUROC was 0.88 (range 0.85 to 0.91) in 6 studies.</td>
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<tr>
<td><strong>Diagnostic accuracy: Hepascore vs. liver biopsy</strong> High For fibrosis, the median AUROC was 0.79 (range 0.69 to 0.82) in 9 studies. For cirrhosis, the median AUROC was 0.89 (range 0.88 to 0.94) in 8 samples reported in 7 studies.</td>
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<tr>
<td><strong>Diagnostic accuracy: Lok Index vs. liver biopsy</strong> Moderate For cirrhosis, the median AUROC was 0.80 (range 0.61 to 0.91) in 8 samples reported in 6 studies. One study reported an AUROC of 0.69 (95% CI 0.69 to 0.74). No study reported the AUROC for the Lok Index for fibrosis.</td>
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<td><strong>Diagnostic accuracy: Pohl Index vs. liver biopsy</strong> Low For severe fibrosis (META VIR F3-F4, Ishak 3-6, or equivalent), 1 study reported an AUROC of 0.53 (95% CI 0.51 to 0.56). For cirrhosis, the AUROC was 0.64 and 0.66 in 2 studies.</td>
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<td><strong>APRI vs. Fibrotest</strong> Moderate Sixteen studies (some of which evaluated overlapping populations) consistently found no differences between the APRI and Fibrotest based on the AUROC.</td>
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<td><strong>AST/ALT ratio vs. other indices</strong> Moderate Twelve of 14 studies found the AST/ALT ratio associated with a lower AUROC compared with various other indices.</td>
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<td><strong>Key Question 4b. What proportion of patients with screen-detected HCV infection receives treatment?</strong> Moderate Three longitudinal studies reported that 15% to 33% of patients with screen-detected chronic HCV infection received treatment.</td>
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<td>Key Question</td>
<td>Strength of Evidence</td>
<td>Summary</td>
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<td>Key Question 5. What are the harms associated with the workup for guiding treatment decisions?</td>
<td>Moderate</td>
<td>One study (n=2,740) of patients with chronic HCV infection and compensated cirrhosis with an Ishak fibrosis score of ≥3 reported serious adverse events in 1.1% of patients, including 0.6% serious bleeds and 0.3% severe pain, with no deaths. Five large (n=1,398 to 61,184) interventions series published since 2004 of patients undergoing percutaneous liver biopsy for a variety of reasons reported peri-procedural mortality in &lt;0.2% and serious complications in 0.3% to 1.0%.</td>
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**Key Question 6a. How effective is counseling or immunization of patients with HCV infection at improving health outcomes or reducing the spread of HCV?**

| Clinical outcomes or spread of disease: Counseling | Insufficient | One randomized trial found a self-management program associated with slight improvements in SF-36 vitality scores compared with provision of educational materials after 6 weeks, but there were no effects on other measures of generic or HCV-related quality of life. |
| Clinical outcomes: Immunization | Insufficient | No studies. |

**Key Question 6b. Does becoming aware of positive HCV infection status decrease high-risk behaviors?**

| High-risk behaviors: Counseling | Insufficient | Three retrospective studies reported substantial reductions in alcohol use following diagnosis of HCV infection, but 2 prospective studies found no evidence of sustained reductions in high-risk behaviors (alcohol use or injection drug use behaviors) following diagnosis. Results from 2 cross-sectional studies were mixed. |

**Key Question 6c. How effective is counseling or immunization of patients with HCV infection at improving intermediate outcomes, including change in high-risk behaviors?**

| Intermediate outcomes: Immunization | Insufficient | No studies. |

**Key Question 7. Do any interventions decrease or increase the vertical transmission of HCV during delivery or in the perinatal period?**

| Vertical transmission: Elective cesarean vs. vaginal delivery | Low | Two good-quality studies found no statistically significant difference in risk of vertical transmission of HCV infection between elective cesarean and vaginal delivery, but trends were in opposite directions. |
| Vertical transmission: Any cesarean vs. vaginal delivery | Moderate | Ten of 11 observational studies (one good quality) found no statistically significant difference in risk of vertical transmission of HCV infection following vaginal compared with cesarean (not specified if elective or emergent) delivery. |
| Vertical transmission: Internal fetal monitoring vs. no internal fetal monitoring | Insufficient | Three observational studies (two good quality) found inconsistent evidence on the association between internal fetal monitoring and the risk of vertical transmission of HCV infection (no association in 2 studies) and OR 6.7 (95% CI 1.1 to 36) in the 3rd study. |
Although screening tests can accurately identify adults with chronic HCV infection, targeted screening strategies based on presence of risk factors misses a substantial proportion of patients with HCV infection. As a result, more research is needed to understand the effects of different screening strategies on clinical outcomes.

Evidence on effects of knowledge of HCV status and counseling and immunizations in patients diagnosed with HCV infection remains sparse. The assessments of benefits and harms of screening are likely to be contingent on the effectiveness of antiviral regimens, which are the subject of a complementary review.

Discussion

Key Findings and Strength of Evidence

Table A summarizes the findings of this review, including strength of evidence grades. Details about factors assessed to determine the overall strength of evidence for each body of evidence are shown in Appendix F. As in the 2004 USPSTF review, we found no direct evidence on benefits of screening for HCV infection compared with no screening in asymptomatic adults without liver enzyme abnormalities. Although direct harms of screening appear minimal (since it is a simple blood test), other harms such as labeling, anxiety, and stigmatization remain poorly studied, though reported in some qualitative and other studies.

Retrospective studies found that screening strategies targeting multiple risk factors were associated with sensitivities of over 90 percent and numbers needed to screen to identify one case of HCV infection of less than 20. More narrowly targeted alternative screening strategies were associated with numbers needed to screen of less than two, but missed up to two-thirds of infected patients. No study prospectively compared different screening strategies or assessed effects of alternative screening strategies on outcomes. Epidemiologic data indicates that about two-thirds of people with chronic HCV infection were born between 1945 and 1965, suggesting that testing of all people in this birth-cohort could be an efficient strategy. However, the only published report on birth-cohort screening is a cost-effectiveness modeling study which did not meet inclusion criteria because it did not assess clinical data.

In the absence of direct evidence on screening, understanding the accuracy of the screening test as well as benefits and harms of subsequent workup and treatments in patients found to be HCV-positive can provide an indirect chain of evidence regarding potential benefits of screening. HCV antibody testing with subsequent polymerase chain reaction testing for circulating virus was found to be accurate for identifying patients with HCV infection in a previous systematic review and diagnostic accuracy was not re-reviewed for this report. Regarding the workup in patients found to be HCV-positive, a number of blood indices were associated with an AUROC of 0.75 to 0.86 to 0.82 for fibrosis (META VIR F2-F4, Ishak 3-6, or equivalent) and 0.80 to 0.91 for cirrhosis (META VIR F4, Ishak 5-6, or equivalent), generally considered “good” to “very good” diagnostic accuracy. Only one study evaluated the clinical impact of no biopsy prior to antiviral treatment, showing no differences compared with patients who underwent biopsy prior to treatment. Harms of biopsy...
appeared to be small, with a risk of death of <0.2 percent and serious complications (primarily bleeding and severe pain) in about 1 percent. However, estimating harms of screening associated with liver biopsy is a challenge. Although clinical practice has evolved toward less routine use of biopsy prior to antiviral therapy, we found no studies reporting current estimates of the proportion of patients who undergo biopsy prior to treatment.

Some evidence published since the 2004 review suggests that patients who become aware of being HCV positive may reduce risky behaviors, but prospective studies suggest that such behavior changes may not be sustained. Evidence on effective methods of counseling to reduce risky behaviors remains sparse, though one randomized trial showed an intervention based on behavioral principles was effective at reducing risky injection drug use behaviors. We did not review evidence on the general effectiveness of counseling and risk prevention interventions in non-HCV infected people. Whether such evidence can be extrapolated to patients with HCV infection requires assumptions regarding applicability. No study has evaluated effects of immunizations for hepatitis A virus (HAV) or hepatitis B virus (HBV) infection on clinical outcomes or effects of counseling or awareness of HCV status on transmission risk.

Many of the benefits from screening are likely to occur as a result of antiviral treatments, which have become increasingly effective at achieving a sustained virologic response (SVR) (a strong predictor of long-term virologic response). Antiviral treatments, including recently approved new regimens, and the association between SVR and improvement in clinical outcomes (a key evidence gap in the 2004 USPSTF review) will be addressed in a separate review. In screened populations, benefits of antiviral treatments will depend in part on the proportion of patients who actually receive treatment. Two studies of screen-detected patients found that 15 to 33 percent of screen-detected patients with chronic HCV infection received antiviral treatment. However, interpreting these findings is a challenge, as the proportion of patients who receive treatment is likely to vary depending on the population studied and criteria used to determine treatment eligibility, which continue to evolve and differ across settings.

No study compared effects of screening with not screening pregnant women. Cohort studies report conflicting information regarding intrapartum management including effects of mode of delivery on transmission risk. Two studies that looked at rupture of membranes, which is most commonly experienced by women intending vaginal delivery, reported increased risk of HCV transmission with more prolonged duration of ruptured membranes. Based on those findings, it would be expected that elective cesarean delivery, in which women undergo planned cesarean (intended to be prior to labor or rupture of membranes) should be associated with decreased risk of vertical transmission; however, studies reported conflicting information, with the largest single study reporting a nonstatistically significant higher trend towards increased transmission following elective cesarean compared with vaginal delivery. Possible explanations include threshold effects (in terms of duration of prolonged rupture of membranes), influence of viral load, or other potential modifying factors in women with ruptured membranes. Studies consistently found no association between breastfeeding and transmission risk.

Findings in Relationship to What Is Already Known

Like an earlier evidence review on HCV screening conducted for the USPSTF, we found no direct evidence on clinical benefits associated with screening compared with no screening. As in that review, we found that screening strategies targeted at people with a history of intravenous drug use are associated with small numbers needed to screen to identify one case of HCV infection, but miss a significant proportion of people screened.

The USPSTF review found HCV screening tests to be accurate and we did not re-review diagnostic accuracy. Consistent with other reviews, we found that noninvasive tests have fair to good accuracy for diagnosing fibrosis and good to excellent accuracy for diagnosing cirrhosis compared to liver biopsy. Estimates of serious harms associated with liver biopsy are also consistent with estimates from the prior USPSTF review.

Evidence showing that knowledge of HCV status or interventions in people with HCV infection is effective at reducing transmission or high-risk behaviors for transmission remains limited. Studies reporting rates of antiviral treatment in screen-detected patients with HCV infection were all published after the USPSTF review, which included studies of referral populations, rather than cohorts of patients identified through screening. The studies of referral populations reported somewhat higher rates of treatment (30–40 percent) compared to the studies of screen-detected patients (15–33 percent) in our review.

The prior USPSTF evidence review did not address prenatal screening for HCV. However, our findings
were similar to a guideline from the American Congress of Obstetricians and Gynecologists (ACOG), which concluded that there are no known effective preventive measures for reducing the risk of mother-to-child transmission of HCV infection.\textsuperscript{51} Like our review, ACOG found limited evidence suggesting a possible association between prolonged rupture of membrane after labor and use of internal fetal monitoring and increased risk of vertical transmission.

**Applicability**

Several issues may limit applicability of our findings to screening settings likely to be encountered in clinical practice. Most of the studies\textsuperscript{64-68} evaluating the sensitivity and yield of different screening strategies (Key Question 2b) were conducted in higher prevalence settings, potentially limiting applicability to average- or low-risk populations.

Few studies evaluating harms of liver biopsy were conducted specifically in populations of patients with HCV infection, and none specifically evaluated a screen-identified cohort. The applicability of estimates of serious harms such as bleeding from such studies to a screen-detected population would depend on the presence and severity of liver disease and other comorbidities in the people who underwent biopsy. For example, patients with end-stage liver disease or undergoing biopsy for hepatocellular carcinoma are likely to be at increased risk for bleeding following liver biopsy compared to asymptomatic patients identified through screening.

Studies reporting rates of antiviral treatment in cohorts of patients with screen-detected HCV infection are also difficult to interpret, as the proportion of patients who receive treatment is likely to vary depending on the population studied and criteria used to determine treatment eligibility, which continue to evolve and differ across settings. In addition, two of the studies were conducted in Veterans Affairs (VA) settings\textsuperscript{83,85} and the third\textsuperscript{84} in people with a history of intravenous drug use (IVDU), and may not accurately reflect treatment patterns in other settings.

Although none of the studies assessing diagnostic accuracy of noninvasive tests compared to liver biopsy were conducted in screen-detected patients, studies generally enrolled a broad spectrum of patients who varied in severity of fibrosis and other markers of HCV infection severity. Therefore, estimates of diagnostic accuracy are likely to be applicable to patients identified by screening.

We did not include evidence on the general effectiveness of interventions to reduce alcohol use or risky injection drug use behaviors, as the applicability of such studies to patients specifically with HCV infection is uncertain. Our findings are not applicable to patients with HIV infection, end-stage renal disease, or following transplant, as these populations were excluded from the review.

Similarly, our findings on the association between labor and delivery management practices and breastfeeding on risk of vertical transmission are not applicable to women with concomitant HIV infection. Risk of mother-to-child transmission of HCV appears to be higher in women with concomitant HIV infection compared to those without HIV infection. Specific interventions already recommended to prevent vertical transmission of HIV infection include antiretroviral therapy, avoidance of breastfeeding, and elective cesarean in selected patients.\textsuperscript{94}

**Implications for Clinical and Policy Decisionmaking**

Our review has some important potential implications for clinical and policy decisionmaking. Because of the lack of direct evidence showing clinical benefits associated with HCV screening, decisions regarding screening must necessarily be made on the basis of the indirect chain of evidence. Evidence clearly supports that HCV antibody tests are accurate for identifying HCV infection, but that strategies targeted at clinical risk factors miss a substantial proportion of infected patients, in part due to undisclosed or unknown risks. Regardless of the screening strategy applied, for screening to be effective, identification of people with HCV infection must lead to subsequent interventions that improve clinical outcomes. Given the lack of evidence showing beneficial effects of screening and subsequent interventions on transmission risk or on intermediate outcomes such as risky behaviors, screening decisions are likely to be critically dependent on the effectiveness of antiviral treatments, which is covered in a separate review.\textsuperscript{53} Therefore, we recommend that decisions about screening should only be made after also considering the evidence on screening and treatment in totality.

In the prenatal setting, no intervention has been clearly demonstrated to reduce the risk of vertical transmission of HCV infection. Nonetheless, until more evidence is available, if a woman with HCV attempts vaginal delivery, clinicians may consider limiting the duration of ruptured membranes to less than 6 hours given some evidence of an association between prolonged rupture of membranes and increased risk of vertical transmission.\textsuperscript{94}

Clinicians and policymakers may consider modeling studies to help estimate potential benefits and harms
of screening. We did not include such studies, whose usefulness will depend on the veracity of the model and the reliability of various input parameters.

Limitations of the Comparative Effectiveness Review Process

We excluded non–English-language articles, which could result in language bias, though we identified no non–English-language studies that would have met inclusion criteria. We included cohort studies on the association between labor and delivery practices or breastfeeding and vertical transmission. Such studies are more susceptible to bias and confounding than well-conducted randomized trials. We therefore focused on results from studies that performed adjustment and were otherwise assessed as being at lower risk of bias. For Key Questions related to effects of knowledge of HCV status or counseling on risky behaviors, we included weaker study designs such as before-after studies and cross-sectional studies due to lack of evidence from studies with stronger designs. We were unable to formally assess for publication bias due to small numbers of studies, methodological shortcomings, and differences across studies in designs, measured outcomes, and other factors. We did not attempt to pool results for any Key Questions due to differences across studies in populations, interventions, and outcomes assessed. Finally, we did not evaluate evidence on potential barriers to screening and how they might affect estimates of benefits and harms.

Limitations of the Evidence Base

The evidence base on HCV screening had a number of important limitations. No direct evidence comparing clinical outcomes in patients screened with those not screened, or clinical outcomes associated with different HCV screening strategies, is available. Studies on the sensitivity and yield of different screening strategies were primarily conducted in higher-prevalence populations. Only one small observational study evaluated clinical outcomes in people who underwent liver biopsy compared to no liver biopsy prior to antiviral treatment. The only studies reporting rates of antiviral treatment in cohorts of patients with screen-identified HCV infection were conducted in VA settings or in a population of IVDUs and may be of limited applicability in other settings. Few studies evaluated the effectiveness of interventions for reducing alcohol use or risky injection drug use behaviors in people specifically with HCV infection. In pregnant women, although studies have evaluated the association between prolonged rupture of membranes and internal fetal monitoring and risk of vertical transmission, no study has evaluated whether interventions to reduce their occurrence are associated with decreased risk.

Research Gaps

Significant research gaps continue to limit full understanding of the benefits and harms of screening for HCV infection. Studies that compare clinical outcomes in patients screened and not screened for HCV infection would provide the most direct evidence, but would require large sample sizes and long duration of followup. However, such studies would not necessarily need to be prospective, as well-conducted retrospective studies could also be informative. In addition, in lieu of direct evidence on effects of screening on clinical outcomes, studies that prospectively evaluate the accuracy and efficiency of alternative screening strategies (such as the CDC birth-cohort approach of screening all adults born between 1945 and 1965) would help fill important research gaps and provide some evidence to help guide strategies for targeted screening. No studies have adequately assessed the harmful impacts due to anxiety, labeling, or relationships with family and sexual partners that may result from screening for HCV infection in these patients and whether these harmful impacts can be minimized by appropriate counseling.

Another important research gap is that although many studies have assessed the diagnostic accuracy of noninvasive tests compared to liver biopsy, there is insufficient evidence to determine effects of foregoing liver biopsy on clinical outcomes. Although liver biopsy is still regarded as the most accurate method for assessing the histologic stage of HCV infection, it is an invasive test with some risk for serious harms, making workup strategies that make use of noninvasive tests with high diagnostic accuracy a potential alternative. Studies that evaluate the outcomes of patients who receive treatment without liver biopsies would be helpful in determining whether all or selected patients should undergo pretreatment biopsy.

Another important research gap is that even though screening for chronic HCV infection may have importance not only in terms of individual clinical outcomes, but also as a public health measure, there is insufficient evidence to determine effects of screening on risk of transmission. In addition, screening might also help identify patients who would benefit from counseling about alcohol use or hepatitis A and B vaccinations, but there is insufficient evidence to determine effects of these interventions.
Studies demonstrating important individual or public health benefits from counseling, immunizations, and following a diagnosis of HCV in asymptomatic patients would help strengthen the case for screening.

In pregnant women, although limited evidence suggests an association between prolonged rupture of membranes and vertical transmission of HCV infection, more studies are needed to understand the strength of the association and whether interventions targeted at avoiding prolonged rupture of membranes are effective at reducing risk of transmission.

Conclusions

Although screening can accurately identify adults with chronic HCV infection, more research is needed to understand the effects of different screening strategies on clinical outcomes. Evidence on effects of knowledge of HCV status and counseling and immunizations in patients diagnosed with HCV infection remains sparse, and more research is needed to understand effective interventions for preventing vertical transmission. A complete assessment of benefits and harms of screening requires consideration of the effectiveness of antiviral regimens, which are the subject of a complementary review.

References


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