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

US Preventive Services Task Force

Et al.

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IMPORTANCE Hepatitis C virus (HCV) is the most common chronic blood-borne pathogen in the US and a leading cause of complications from chronic liver disease. HCV is associated with more deaths than the top 60 other reportable infectious diseases combined, including HIV. Cases of acute HCV infection have increased approximately 3.8-fold over the last decade because of increasing injection drug use and improved surveillance.

OBJECTIVE To update its 2013 recommendation, the USPSTF commissioned a review of the evidence on screening for HCV infection in adolescents and adults.

POPULATION This recommendation applies to all asymptomatic adults aged 18 to 79 years without known liver disease.

EVIDENCE ASSESSMENT The USPSTF concludes with moderate certainty that screening for HCV infection in adults aged 18 to 79 years has substantial net benefit.

RECOMMENDATION The USPSTF recommends screening for HCV infection in adults aged 18 to 79 years. (B recommendation)

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Summary of Recommendation

The USPSTF recommends screening for hepatitis C virus (HCV) infection in adults aged 18 to 79 years.	B

See the Figure for a more detailed summary of the recommendation for clinicians. USPSTF indicates US Preventive Services Task Force.

Importance

Hepatitis C virus (HCV) is the most common chronic blood-borne pathogen in the US and a leading cause of complications from chronic liver disease.[1] Hepatitis C virus infection is associated with more deaths than the top 60 other reportable infectious diseases combined, including HIV.[2] The most important risk factor for HCV infection is past or current injection drug use.[1] In the US, an estimated 4.1 million persons have past or current HCV infection (ie, they test positive for the anti-HCV antibody). Of these persons who test positive for the anti-HCV antibody, approximately 2.4 million have current infections based on testing with molecular assays for HCV RNA.[1,3-5] The estimated prevalence of chronic HCV infection is approximately 1.0% (2013 to 2016).[6] An estimated 44 700 new HCV infections occurred in the US in 2017.[7] Cases of acute HCV infection have increased approximately 3.8-fold (2010 to 2017) over the last decade because of increasing injection drug use and improved surveillance.[7] The most rapid increase in acute HCV incidence has been in young adults aged 20 to 39 years who inject drugs, with increases in both sexes but more pronounced in men.[7] Rates increased especially in American Indian/Alaskan Native and non-Hispanic white populations.[7]

Assessment of Magnitude of Net Benefit

The US Preventive Services Task Force (USPSTF) concludes with moderate certainty that screening for HCV infection in adults aged 18 to 79 years has **substantial net benefit**.

See the **Figure** and **Table** for more information on the USPSTF recommendation rationale and assessment. For more details on the methods the USPSTF uses to determine net benefit, see the USPSTF Procedure Manual.[8]

Practice Considerations

Patient Population Under Consideration

This recommendation applies to all asymptomatic adults aged 18 to 79 years without known liver disease.

Figure. Clinical Summary: Screening for Hepatitis C Virus Infection in Adolescents and Adults

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What does the USPSTF recommend?	**For adults aged 18 to 79 years: Grade B** Screen adults for hepatitis C virus (HCV) infection.
To whom does this recommendation apply?	All asymptomatic adults (including pregnant persons) aged 18 to 79 years without known liver disease.
What's new?	This recommendation expands the population that should be screened. The USPSTF now recommends that all adults aged 18 to 79 years be screened. Previously, it recommended screening adults born between 1945 and 1965 and others at high risk.
How to implement this recommendation?	**Screen.** Screen adults aged 18 to 79 years with anti-HCV antibody testing followed by confirmatory polymerase chain reaction testing. a. The USPSTF also suggests that clinicians consider screening persons younger than 18 years and older than 79 years who are at high risk for infection (eg, those with past or current injection drug use). Adults with a positive screening test result are usually followed up with a diagnostic evaluation using one of various noninvasive tests. Treatment typically consists of oral direct-acting antiviral regimens for 8 to 12 weeks. Important considerations include • Communicating that screening is voluntary and undertaken only with the patient's knowledge • Informing patients about HCV infection, how it can (and cannot) be acquired, the meaning of positive and negative test results, and the benefits and harms of treatment • Providing patients the opportunity to ask questions and to decline screening
How often?	One-time screening for most adults. Periodically screen persons with continued risk for HCV infection (eg, persons with past or current injection drug use). There is limited evidence to determine how often to screen persons at increased risk.
What are other relevant USPSTF recommendations?	The USPSTF has made recommendations on screening for hepatitis B virus infection in pregnant persons, hepatitis B virus infection in adults, and HIV infection. These recommendations are available at https://www.uspreventiveservicestaskforce.org.
Where to read the full recommendation statement?	Visit the USPSTF website to read the full recommendation statement. This includes more details on the rationale of the recommendation, including benefits and harms; supporting evidence; and recommendations of others.

The USPSTF recognizes that clinical decisions involve more considerations than evidence alone. Clinicians should understand the evidence but individualize decision-making to the specific patient or situation.

USPSTF indicates US Preventive Services Task Force.

Assessment of Risk

Although all adults aged 18 to 79 years should be screened, a number of risk factors increase risk. The most important risk factor for HCV infection is past or current injection drug use. In the US, recent increases in HCV incidence have predominantly been among young persons who inject drugs (PWID).[1,9] Approximately one-third of PWID aged 18 to 30 years are infected with HCV, and 70% to 90% of older PWID are infected.[9] Clinicians may want to consider screening in adolescents younger than 18 years and in adults older than 79 years who are at high risk (eg, past or current injection drug use).

Pregnant adults should be screened. HCV prevalence has doubled in women aged 15 to 44 years from 2006 to 2014.[1,10,11] From 2011 to 2014, 0.73% of pregnant women tested had an HCV infection, with a 68% increase in the proportion of infants born to HCV-infected mothers.[1,10] Approximately 1700 infected infants are born annually to 29 000 HCV-infected mothers.[1,11] Because of the increasing prevalence of HCV in women aged 15 to 44 years and in infants born to HCV-infected mothers, clinicians may want to consider screening pregnant persons younger than 18 years.

Screening Tests

Screening with anti-HCV antibody testing followed by polymerase chain reaction testing for HCV RNA is accurate for identifying patients with chronic HCV infection.[9] Currently, diagnostic evaluations are often performed with various noninvasive tests that have lower risk for harm than liver biopsy for diagnosing fibrosis stage or cirrhosis in persons who screen positive.[12]

Among patients with abnormal results on liver function tests (measurement of aspartate aminotransferase, alanine aminotransferase, or bilirubin levels) who were tested for reasons other than HCV screening, finding the cause of the abnormality often includes testing for HCV infection and is considered case finding rather than screening; therefore, it is outside the scope of this recommendation.

Screening Intervals

Most adults need to be screened only once. Persons with continued risk for HCV infection (eg, PWID) should be screened periodically. There is limited information about the specific screening interval that should occur in persons who continue to be at risk for new HCV infection or how pregnancy changes the need for additional screening.

Screening Implementation

Important considerations for implementation of screening include (1) communicating to patients that screening is voluntary and undertaken only with the patient's knowledge and understanding that

Table. Summary of USPSTF Rationale for Screening for Hepatitis C Virus Infection[a]

Rationale	Assessment
Detection	• There is adequate evidence that HCV testing (screening for the anti-HCV antibody followed by confirmation of active infection by HCV RNA assay for persons who test positive) accurately detects HCV infection • There is adequate evidence for 1-time testing in all adults and periodic testing in persons at continued risk of new HCV infection • There is inadequate evidence on the timing of repeat testing
Benefits of early detection and treatment (based on direct or indirect evidence)	• There is no direct evidence on the benefit of screening for HCV infection on health outcomes in asymptomatic adults. There is inadequate direct evidence on the effect of treatment on health outcomes in adults and adolescents. However, there is convincing evidence that the newer DAA regimens result in SVR in a very high proportion (>95%) of adults aged 18 to 79 y and adequate evidence of SVR in adolescents. • There is adequate evidence of a consistent association between SVR after antiviral therapy and improved health outcomes (decreased risk of all-cause mortality, mortality due to liver disease, cirrhosis, and hepatocellular carcinoma) • Given the accuracy of the screening test and the availability of effective interventions for HCV infection, the USPSTF determined that the indirect evidence is adequate that the magnitude of the benefit of screening and treatment is substantial for adults aged 18 to 79 y
Harms of early detection and treatment	• Potential harms of screening include anxiety, patient labeling, and feelings of stigmatization. There is inadequate direct evidence on the harms of screening for HCV infection. • Currently recommended DAA regimens are associated with fewer harms than older interferon-containing therapies, and treatment duration is shorter at 8 to 12 weeks. There is adequate evidence that DAA regimens are associated with low rates of serious adverse effects and withdrawal due to adverse effects. • There is adequate evidence to bound the overall harms of screening and treatment as small based on the known harms of treatment, the high accuracy of screening, and the low likelihood of harms from a blood draw
USPSTF assessment	• The USPSTF concludes with moderate certainty that screening for HCV infection in adults aged 18 to 79 y has substantial net benefit

Abbreviations: DAA, direct-acting antiviral; HCV, hepatitis C virus; SVR, sustained virologic response; USPSTF, US Preventive Services Task Force.

[a] See the eFigure in the Supplement for explanation of USPSTF grades and levels of evidence.

HCV screening is planned; (2) informing patients about HCV infection, how it can (and cannot) be acquired, the meaning of positive and negative test results, and the benefits and harms of treatment; and (3) providing patients the opportunity to ask questions and to decline screening.

Some health care systems serving insured populations, some academic medical centers, and the Veterans Health Administration have achieved high rates of HCV screening and treatment. However, national HCV screening rates in community health centers and from the National Health Interview Study were 8.3% and 17.3%, respectively; 1 study of 4 safety-net primary care practices serving low-income and uninsured or underserved populations found that only 0.8% of persons born in 1945 through 1965 were screened over a 1-year period.[13] Implementation of successful screening may require addressing various barriers to screening and treatment in diverse populations, such as the uninsured.

Treatment

The purpose of antiviral treatment regimens for HCV infection is to prevent long-term health complications of chronic HCV infection (eg, cirrhosis, liver failure, and hepatocellular carcinoma).

Currently, all oral direct-acting antiviral (DAA) regimens without interferon have been accepted as the standard treatment for chronic HCV infection. Antiviral therapy is not generally considered during pregnancy because of the lack of data on the safety of newer DAA regimens during pregnancy and breastfeeding.[14,15]

Additional Tools and Resources

The Centers for Disease Control and Prevention provides strategies for implementing a testing program and additional risk factors at https://www.cdc.gov/hepatitis/hcv/guidelinesc.htm.[16]

Other Related USPSTF Recommendations

The USPSTF has made recommendations on screening for hepatitis B virus infection in pregnant persons,[17] screening for hepatitis B virus infection in adults,[18] and screening for HIV infection.[19]

Update of Previous USPSTF Recommendation

This recommendation incorporates new evidence and replaces the 2013 USPSTF recommendation, which recommended screening for HCV infection in persons at high risk for infection and 1-time screening in adults born between 1945 and 1965 (B recommendation).[20] The new USPSTF recommendation expands the ages for screening to all adults from 18 to 79 years.

The treatment of HCV continues to evolve, resulting in greater benefits and fewer harms than when the USPSTF last considered the evidence. Direct-acting antiviral regimens are of shorter duration, with higher rates of sustained virologic response (SVR) and fewer serious harms than previous treatment regimens. Since 2013, the prevalence of HCV infection has increased in younger persons aged 20 to 39 years. There are limited epidemiologic data available on HCV incidence in adolescents younger than 18 years. The HCV infection prevalence rates in older adults born between 1945 and 1965 remain relatively high, and prevalence in the elderly will increase as this population ages. Clinical trials of DAA treatment included adults in their early 80s, which increases the evidence for the benefits of screening in older adults. In addition, many older adults could experience the benefits of screening. As a result, the USPSTF concluded that broadening the age for HCV screening beyond its previous recommendation will identify infected patients at earlier stages of disease who could greatly benefit from effective treatment before developing complications.

Supporting Evidence

Scope of Review

The USPSTF commissioned a systematic evidence review to update its prior review (from 2013) on screening for HCV infection.[20,21] The scope of this review is similar to that of the prior systematic review, except in the current review, the USPSTF also examined the

evidence on adolescents.[21] For treatment, the USPSTF focused on currently recommended DAA regimens.

Accuracy of Screening Tests and Risk Assessment

The USPSTF previously found HCV screening to be highly accurate.[20] The USPSTF found no new evidence on the yield of repeat vs 1-time screening or alternative screening strategies (eg, different risk- or prevalence-based methods).

Benefits of Early Detection or Treatment

The USPSTF found no direct evidence on the benefits of HCV screening vs no screening on health outcomes or the effects of prenatal HCV screening on the risk of vertical transmission.[1] Treatment studies focused on populations without cirrhosis who are more likely to be asymptomatic and identified by screening. Of the trials of DAA regimens (n = 7167; 26% to 69% female; mean age, 45 to 62 years), 14 were multinational; 11 were conducted in the US or Canada; and the remainder were conducted in New Zealand, Egypt, France, or Asia. In 29 trials, 60% to 100% of patients were white.[1] The trials evaluated a variety of DAA regimens recommended in current guidelines. Treatment duration was 12 weeks in all but 2 trials, which allocated patients to either 8 or 12 weeks of treatment. Eleven trials were of good quality and 22 were of fair quality. Forty-nine trials found DAA regimens to be associated with pooled SVR rates ranging from 95.5% to 98.9% across genotypes. Evidence was greatest for genotype 1 infection (32 trials), the most frequent genotype in the US.[1] Sustained virologic response rates were similar in trials that stratified patients according to age, sex, race/ethnicity, or treatment experience with non-DAA regimens.[1]

Direct evidence on the effects of current DAA regimens on health outcomes is limited.[1] Pooled analysis from 10 trials found small, short-term improvements in quality of life scale scores after treatment with a DAA regimen compared with baseline scores.[1] Trials reporting short-term mortality (<1 year) found few events and were not designed to detect differences in mortality rates. Twenty-one trials reported no deaths; in the other 10 trials, there were 17 deaths (0.4% [17/3848] overall).[1]

The USPSTF review evaluated the linkage between achieving SVR after antiviral therapy vs no SVR and health outcomes. Sustained virologic response after antiviral therapy was consistently associated with decreased risk of all-cause mortality (13 studies; pooled hazard ratio [HR], 0.40 [95% CI, 0.28-0.56]), liver mortality (4 studies; pooled HR, 0.11 [95% CI, 0.04-0.27]), cirrhosis (4 cohorts in 3 studies; pooled HR, 0.36 [95% CI, 0.33-0.40]), and hepatocellular carcinoma (20 studies; pooled HR, 0.29 [95% CI, 0.23-0.38]) vs no SVR, after adjustment for potential confounders.[1]

The USPSTF found limited new evidence on the risk of vertical transmission. Five observational studies found no clear association between risk of vertical transmission of HCV infection and the mode of delivery.[21] One good-quality US study showed that prolonged rupture of membranes (>6 hours) was associated with increased risk of HCV transmission in 189 mother-infant pairs compared with membrane rupture lasting less than 6 hours (adjusted odds ratio, 9.3 [95% CI, 1.5-180]).[1,22] One observational study in 188 mother-infant pairs found that internal fetal monitoring was associated with an increased risk of vertical transmission of HCV infection compared with external monitoring (adjusted odds ratio, 6.7 [95% CI, 1.1-35.9]).[1,22] Three observational studies did not find a clear association between breastfeeding and an increased risk of vertical transmission of HCV infection.[1]

The evidence is also limited in adolescents. Seven trials (n = 300) reported SVR rates in adolescents taking DAA regimens similar to those taken by adults (97%-100%).[1] However, some of the trials evaluated regimens that are not approved by the US Food and Drug Administration for use in adolescents.[1] Direct-acting antiviral regimens recommended and approved by the US Food and Drug Administration for use in adolescents are ledipasvir/sofosbuvir, sofosbuvir/ribavirin, and glecaprevir/pibrentasvir.[1] The evidence on antiviral treatment and health outcomes in adolescents is very limited. One post hoc before-and-after analysis found that scores based on the Pediatric Quality of Life Inventory (ie, school and social functioning) improved from baseline to 24 weeks after treatment with a DAA regimen.[1]

Modeling studies that compared screening in all persons 18 years and older with birth cohort screening suggested that expanded screening strategies would be beneficial, despite different assumptions regarding chronic HCV infection progression and rates of linkage to care.[1] One analysis of a hypothetical cohort of the US population used more conservative assumptions and found that screening everyone 18 years and older would identify an estimated 256 000 additional HCV cases and lead to an estimated 280 000 additional individuals who achieve SVR and an estimated 4400 fewer cases of hepatocellular carcinoma over a lifetime.[1,23]

Harms of Screening or Treatment

The USPSTF did not identify any new studies providing direct evidence on screening harms. Poor-quality evidence from the prior review suggested potential negative psychological and social effects from HCV screening.[1,24]

Direct-acting antiviral regimens are associated with fewer harms than older interferon-containing therapies. Treatment duration has shortened from 24 to 48 weeks with older interferon-containing regimens to 8 to 12 weeks.[1] In DAA trials (33 trials; n = 7167) with adverse event data, the pooled rate of any adverse event was 73.3%.[1] Rates of serious adverse events (1.9%) and withdrawal due to adverse events (0.4%) were low compared with rates reported for interferon-containing regimens.[1] Pooled rates of specific adverse events ranged from 2.4% for anemia to 18.4% for headache and were also lower when compared with rates reported for older interferon-containing therapies.[1] The most common adverse events were fatigue, headache, nausea, and diarrhea.[1]

Seven nonrandomized, open-label trials (n = 300) in adolescents examined treatment harms. Five trials reported no withdrawals due to adverse events; 1 trial reported a serious adverse event (grade 3 joint injury). The rate of any adverse event was 27% in 1 trial and 71% to 84% in 4 trials. Specific adverse event rates across trials ranged from 3% to 48% for headache (7 trials), 5% to 53% for fatigue (7 trials), and 3% to 28% for gastrointestinal adverse events (nausea, vomiting, or diarrhea) (5 trials).[1] Three trials reported no deaths in adolescents (n = 182) treated with DAA regimens.[1] These trials were not designed to evaluate long-term harms associated with DAA treatment during adolescence.[1]

Response to Public Comment

A draft version of this recommendation statement was posted for public comment on the USPSTF website from August 27 to

September 23, 2019. Some comments asked for a definition of "high risk"; however, an extensive list of risk factors is beyond the scope of this recommendation statement. The Additional Tools and Resources section provides a link to other resources. Some comments expressed concern about the lack of guidance on screening intervals for pregnant adults. In response, the USPSTF added language to the Practice Considerations section. Some comments raised concerns about implementation. In response, the USPSTF added language about counseling and consent to the Screening Implementation section. Some comments urged more research on the benefits and harms of treatment in pregnant adults. The USPSTF clarified its call for research in pregnant persons in the Research Needs and Gaps section.

Research Needs and Gaps

Addressing several key research gaps could help inform the benefit of screening for HCV infection in US-based populations:

- Research is needed on the yield of repeat vs 1-time screening for HCV and different repeat screening intervals to inform recommendations on optimal screening intervals for persons at high risk.
- Research is needed to identify labor management practices (eg, prolonged rupture of membranes or use of internal fetal monitoring) and treatment of HCV infection prior to pregnancy to reduce the risk of mother-to-child transmission. Research is also needed on the benefits and harms of additional screening during pregnancy for low-risk persons who have been previously screened.
- Trials and cohort studies that measure effects on quality of life, function, and extrahepatic effects of HCV infection (eg, renal function, cardiovascular effects, or diabetes) would be helpful for evaluating the effects of DAA regimens on short-term health outcomes.
- Additional studies are needed to examine the epidemiology of HCV infection and the effectiveness of DAA regimens in adolescents.

Recommendations of Others

The Centers for Disease Control and Prevention is in the process of updating its HCV screening guidelines. Its draft screening guideline recommends screening for HCV at least once in a lifetime for all adults 18 years and older, except in settings where the prevalence is less than 0.1%. All pregnant persons should be screened for HCV during each pregnancy, except in settings where the prevalence of HCV infection is less than 0.1%. All persons with risk factors (eg, persons with HIV, prior recipients of blood transfusions, persons who ever injected drugs and shared needles, and persons who are born to an HCV-infected mother) should be tested for HCV, with periodic testing while risk factors persist.[25] The American College of Obstetricians and Gynecologists recommends offering HCV screening to pregnant persons with risk factors.[26] The American Association for the Study of Liver Diseases and the Infectious Diseases Society of America recommends 1-time routine, opt-out HCV screening for all persons 18 years and older and 1-time testing for all persons younger than 18 years at increased risk of HCV exposure. They also recommend periodic testing for persons with an increased risk of HCV exposure and annual HCV testing for all PWID and for HIV-infected men who have unprotected sex with men.[27]

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