Draft Recommendation Statement

Hepatitis C Virus Infection in Adolescents and Adults: Screening

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Draft: Recommendation Summary

Population	Recommendation	Grade (What's This?)
Adults ages 18 to 79 years	The USPSTF recommends screening for hepatitis C virus (HCV) infection in adults ages 18 to 79 years.	

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In an effort to maintain a high level of transparency in our methods, we open our draft Recommendation Statements to a public comment period before we publish the final version.

Comment period is not open at this time.

Draft: Preface

The U.S. Preventive Services Task Force (USPSTF) makes recommendations about the effectiveness of specific preventive care services for patients without obvious related signs or symptoms.

It bases its recommendations on the evidence of both the benefits and harms of the service and an assessment of the balance. The USPSTF does not consider the costs of providing a service in this assessment.

The USPSTF recognizes that clinical decisions involve more considerations than evidence alone. Clinicians should understand the evidence but individualize decisionmaking to the specific patient or situation. Similarly, the USPSTF notes that policy and coverage decisions involve considerations in addition to the evidence of clinical benefits and harms.

Draft: Importance

HCV is the most common chronic bloodborne pathogen in the United States and a leading cause of complications from chronic liver disease.[1] HCV 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 United States, an estimated 4.1 million persons have past or current HCV infection (i.e., tests positive for the anti-HCV antibody). Of these persons with antibodies, 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 41,200 new HCV infections occurred in the United States in 2016.[7] Cases of acute HCV infection have increased approximately 3.5-fold (2010 to 2016) over the last decade.[7] The increase in acute HCV incidence has mostly affected young, white persons who inject drugs (PWID), especially those living in rural areas.[8-10] There has also been an increase in the number of women ages 15 to 44 years with HCV infection.[11, 12]

Draft: Assessment of Magnitude of Net Benefit

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

See the Table for more information on the USPSTF recommendation rationale and assessment.

For more details on the methods the USPSTF uses to determine the net benefit, see the USPSTF Procedure Manual.[13]

Draft: Practice Considerations

Patient Population Under Consideration

This recommendation applies to all asymptomatic adults without known liver disease.

Assessment of Risk

Although all adults ages 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 United States, recent increases in HCV incidence have predominantly been among young persons who inject drugs (PWID).[1, 14] Approximately one-third of PWID ages 18 to 30 years are infected with HCV, and 70% to 90% of older PWID are infected.[14] Clinicians may want to consider screening in adolescents younger than age 18 years and in adults older than age 79 years who are at high risk.

Pregnant adults should be screened. HCV prevalence has doubled in women ages 15 to 44 years from 2006 to 2014.[1, 11, 12] 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, 11] Approximately 1,700 infected infants are born annually to 29,000 HCV-infected mothers.[1, 12] Due to the increasing prevalence of HCV in women ages 15 to 44 years and in infants born to HCV-infected mothers, clinicians may want to consider screening pregnant persons younger than age 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.[14] Currently, diagnostic evaluations are often performed with various noninvasive tests as possible alternatives to liver biopsy for diagnosing fibrosis stage or cirrhosis to reduce overall harms in persons who screen positive.[15]

Among patients with abnormal results on liver function tests (measurement of aspartate aminotransferase, alanine aminotransferase, or bilirubin) 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 only be screened once. Persons with continued risk for HCV infection (e.g., 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.

Screening Implementation

The USPSTF believes that screening should be voluntary and undertaken only with the patient's knowledge and understanding that HCV screening is planned.

Treatment

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

Currently, all oral direct-acting antiviral (DAA) regimens without interferon have been accepted as the standard treatment of 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.[16, 17]

Other Related USPSTF Recommendations

The USPSTF has made recommendations on screening for hepatitis B virus infection in pregnant persons, screening for hepatitis B virus infection in adults, and screening for HIV infection.[18-20]

Draft: 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 one-time screening for HCV infection in adults born between 1945 and 1965 (Grade B).[21] The Task Force's new recommendation expands the ages for screening to all adults.

The treatment of HCV continues to evolve, resulting in greater benefits and fewer harms than when the USPSTF last considered the evidence. DAA 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. 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. There is limited epidemiologic data available on HCV incidence in adolescents younger than age 18 years. 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.

Draft: Supporting Evidence

Scope of Review

The USPSTF commissioned a systematic evidence review to update its prior U.S. Preventive Services Task Force (USPSTF) review on screening for HCV infection.[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. 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 .[14] The USPSTF found no new evidence on the yield of repeat versus one-time screening or alternative screening strategies (e.g., different risk- or prevalence-based methods).

Benefits of Early Detection or Treatment

The USPSTF found no direct evidence on the benefits of HCV screening versus 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=7,167; 26%-69% female; mean age, 45 to 62 years), 14 were multinational; 11 were conducted in the United States 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 two trials, which allocated patients to either 8 or 12 weeks of treament. Eleven trials were of good quality and 22 were of fair quality. Forty-nine trials found DAA regimens associated with pooled SVR rates that ranged from 95.5% to 98.9% across genotypes. Evidence was greatest for genotype 1 infection (32 trials), the most frequent genotype in the United States.[1] SVR 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% [17/3,848] overall).[1]

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

The USPSTF found that new evidence on the risk of vertical transmission is limited. Five observational studies found no clear association between risk of vertical transmission of HCV infection and the mode of delivery.[1] One good-quality U.S. study showed that prolonged rupture of membranes (more than 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 to 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 to 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]

In adolescents, the evidence is also limited. Seven trials (n=300) reported SVR rates in adolescents taking DAA regimens similar to those used in adults (97% to 100%).[1] However, some of the trials evaluated regimens that are not approved by the U.S. Food and Drug Administration for use in adolescents.[1] DAA regimens recommended and approved by the U.S. 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 (i.e., school and social functioning) improved from baseline to 24 weeks after treatment with a DAA regimen.[1]

Modeling studies that compared screening of all persons age 18 years and older with birth cohort screening suggested that expanded screening strategies would be beneficial despite different assumptions regarding chronic HCV infection progression, costs of DAA therapy, and rates of linkage to care.[1] One analysis of a hypothetical cohort of the U.S. population used more conservative assumptions and found that screening everyone age 18 years and older would identify 256,000 additional HCV cases and lead to 280,000 additional cures and 4,400 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]

DAA regimens are associated with fewer harms than older interferon-containing therapies. Duration of treatment is also shorter at 8 to 12 weeks compared with older interferon-containing regimens (24 to 48 weeks).[1] In DAA trials (33 trials; n=7,167) 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 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 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; one trial reported a serious adverse event (grade 3 joint injury). The rate of any adverse event was 27% in one trial and 71% to 84% in four 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]

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Draft: Research Needs and Gaps

There are several key research gaps that could help inform the benefit of screening for HCV infection in U.S.-based populations:

- Research is needed on the yield of repeat versus one-time screening for HCV and different repeat screening intervals to inform recommendations on optimal screening intervals.
- Research is needed to identify labor management practices (e.g., 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.
- Trials and cohort studies that measure effects on quality of life, function, and extrahepatic effects of HCV infection (e.g., renal function, cardiovascular effects, or diabetes) would be helpful for evaluating the impact 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.

Draft: Recommendations of Others

The Centers for Disease Control and Prevention recommends screening in high-risk patients and age cohort–based screening for HCV in all persons born between 1945 and 1965.[25] The CDC and the American College of Obstetricians and Gynecologists recommend offering HCV screening to pregnant persons with risk factors.[26, 27] The American Association for the Study of Liver Diseases, the Infectious Diseases Society of America, and the American College of Gastroenterology recommend screening for HCV infection in higher-risk patients.[28, 29]

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Draft: Table. Summary of USPSTF Rationale

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 for persons who test positive) accurately detects HCV infection. • There is adequate evidence for one-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 in asymptomatic adults on health outcomes. 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 ages 18 to 79 years 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 ages 18 to 79 years.
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 ages 18 to 79 years has substantial net benefit.

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