# Screening and diagnosis of chronic hepatitis C virus infection

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## INTRODUCTION

As chronic infection with hepatitis C virus (HCV) is often asymptomatic, screening is necessary to identify most patients with infection. The diagnosis of HCV infection is based on detection of antibodies to HCV as well as viral RNA.

This topic will review the rationale for screening and the approach to diagnostic testing for chronic HCV infection.

Other issues related to chronic HCV infection are discussed elsewhere. (See "Epidemiology and transmission of hepatitis C virus infection" and "Clinical manifestations and natural history of chronic hepatitis C virus infection" and "Overview of the management of chronic hepatitis C virus infection".)

The diagnosis of acute HCV infection is also discussed elsewhere. (See "Clinical manifestations, diagnosis, and treatment of acute hepatitis C virus infection in adults", section on 'Diagnosis'.)

## WHOM TO TEST

**Routine one-time screening for adults** — We suggest all adults ≥18 years of age be screened at least once for chronic HCV infection ( algorithm 1). This approach is consistent with recommendations issued by the United States Centers for Disease Control and Prevention (CDC)

in 2020 [1]. In addition, the CDC advises HCV screening except in settings where HCV prevalence is <0.1 percent; in the absence of HCV prevalence data, the CDC advises universal HCV screening pending availability of such data. The CDC recommendations differ from the 2020 statement from the United States Preventive Services Task Force (USPSTF), which includes an upper age limit of 79 years for universal screening; for individuals ≥80 years, the USPSTF favors screening for those with risk factors for HCV infection (eg, injection drug use, prior receipt of potentially contaminated blood products) and who would be expected to benefit from antiviral therapy based on their comorbidities and life expectancy [2].

Some individuals with ongoing risk for HCV infection should undergo repeat screening. (See 'Those with ongoing risk' below.)

The approach to testing for HCV screening is discussed elsewhere. (See 'Initial testing' below.)

Previously, we had suggested HCV screening among patients who had specific risk factors for infection, belonged to high-prevalence groups (eg, individuals who were in the United States and born between 1945 and 1965, who have HIV infection, who have past or present use of chronic hemodialysis, who were currently or previously incarcerated, who were men who have sex with men), or reside in a high-prevalence country.

Other organizations have guidelines for HCV testing. These include the World Health Organization (WHO), the American Association for the Study of Liver Diseases/Infectious Diseases Society of America joint guideline group, the European Association for the Study of the Liver, the National Health Service in the United Kingdom, the Canadian Task Force on Preventive Health Care, the Canadian Association for the Study of the Liver, and several expert groups in the United States. All recommend screening patients at increased individual risk for HCV (eg, those with a history of injection drug use). However, some guidelines differ in the specification of additional exposures that warrant screening and some also endorse universal screening. As an example, the WHO recommends routine HCV screening in countries with seroprevalence ≥2 percent [3]. In Georgia, a country with a high prevalence of HCV infection, provision of free HCV testing for all adults is a primary component of its HCV elimination plan [4,5].

Links to these and other guidelines can be found below. (See 'Society guideline links' below.)

**Rationale** — As above, we screen all adults at least once for HCV infection ( algorithm 1) (see 'Routine one-time screening for adults' above). HCV infection is a global health problem that can progress to cirrhosis and end-stage liver disease in a substantial proportion of patients. In most countries around the world, increasingly effective and well-tolerated agents are available to treat infection and reduce complications. However, because it is frequently asymptomatic, many

individuals do not know they have chronic HCV infection. In a survey performed in the United States from 2013 to 2016, only 56 percent of persons with HCV infection reported having been told they had hepatitis C [6]. (See "Clinical manifestations and natural history of chronic hepatitis C virus infection".)

Therefore, strengthened guidance for universal hepatitis C testing is warranted. Failure to identify infected individuals is a major bottleneck to linkage to care and successful control of HCV [7]. By improving the detection and ultimately treatment rates of individuals with infection, screening is an important component of successful elimination of HCV for the individual and for public health purposes.

Although there are limited studies directly informing the clinical outcomes with one-time screening for all adults, our approach is supported by the substantial individual benefit of treatment of HCV infection, the minimal harms of screening, and the limitations of risk-based screening in identifying patients with infection.

**Individual benefit of early detection** — With the availability of highly effective, well-tolerated, all-oral antiviral regimens, the vast majority of individuals with HCV infection can be successfully treated with only mild side effects. Identification and successful treatment of HCV infection prior to the development of complications result in decreased all-cause mortality, liver-related death, need for liver transplantation, hepatocellular carcinoma rates, and liver-related complications. (See "Patient evaluation and selection for antiviral therapy for chronic hepatitis C virus infection", section on 'Benefits of treatment'.)

However, without screening, many patients with HCV infection are identified late. As an example, in a large observational cohort study of over 6000 individuals in the United States who had a defined date of HCV diagnosis, 17 percent had a "late diagnosis" of HCV (defined by cirrhosis at the time of diagnosis and/or hepatic decompensation within one year of diagnosis) despite being in health care a mean of six years prior to diagnosis [8]. Late diagnosis was associated with hospitalization and death. Late diagnosis has also been associated with rising rates of hepatocellular cancer requiring liver transplantation in individuals born between 1945 and 1965 in the United States (ie, baby boomers) [9].

**Limitations of risk-based screening** — The prevalence of HCV is higher among patients who have established risk factors for infection, and risk-based screening can be a sensitive method for detecting individuals with chronic HCV infection. However, screening only those who have risk factors falls short for several reasons and thus has given way to more broadly screening birth cohorts (ie, individuals born between certain years) and ultimately screening all adults between the ages of 18 to 79 years. Risk factors for HCV infection are discussed in detail

elsewhere. (See "Epidemiology and transmission of hepatitis C virus infection", section on 'Routes of transmission'.)

The potential benefits of risk-based screening were highlighted in a systematic review of three observational studies among high-prevalence populations (4.6 to 8.3 percent HCV prevalence) [10]. The risks included in the screening strategies varied by study, but most included injection drug use, blood transfusion before 1992, sexual intercourse with an injection drug user, and abnormal liver enzyme levels. Strategies that screened patients with at least one of these risk factors were associated with sensitivities greater than 90 percent and numbers needed of 9 to 18 to identify one case. Risk factors were common in these high-prevalent populations; restricting screening to only those with a history of injection drug use would have lowered the number needed to screen but missed up to two-thirds of infected patients. Among a lower prevalence population (1 percent), which also had a lower prevalence of risk factors, the sensitivity of risk-based screening was 90 percent, with a number needed to screen of 2.4.

However, many individuals with HCV infection do not remember or report having specific risk factors for infection [11,12]. As an example, in an analysis of data from a national health survey, 45 percent of individuals with evidence of HCV infection reported no known exposure risk [11].

Furthermore, even among individuals with high-risk exposure to HCV, many remain untested [13-15]. This was illustrated by a study in which 1033 injection drug users had a reactive HCV antibody on trial enrollment testing, but only 28 percent of them were previously aware of their diagnosis [13]. Similarly, in a study of HCV screening within a managed care network that included over 550,000 adults, only 29 percent of those who had at least one identifiable HCV risk factor had undergone testing for HCV [14].

Even among patients who have documentation of elevated transaminases, an objective finding not subject to limitations of patient recall and reporting, the rate of HCV testing is suboptimal. In a study of patients seen at four large health care organizations throughout the United States, only 44 percent of those who had two or more elevated alanine aminotransferase (ALT) values were subsequently tested for HCV [16].

**Limitations of birth-cohort screening** — In order to overcome the limitations of risk-based screening, several expert organizations in the United States and Canada recommended screening patients born at a specific time (ie, between 1945 and 1965 in the United States and between 1945 and 1975 in Canada) [17,18]. However, with evolving epidemiology of HCV infection, large proportions of infected individuals may be missed by focusing on specific birth cohorts.

Earlier data had suggested that individuals born between those years represented a disproportionate percentage of the total population of adults with chronic HCV infection. In the United States, such individuals accounted for 81 percent of the total estimated population of chronically infected adults, and the birth cohort had an estimated 2.6 percent prevalence of HCV RNA positivity, which was six times higher than that among individuals born in other years [19]. The utility of birth cohort screening was illustrated by a study of over 4700 patients presenting to an urban emergency department in Maryland, in which antibody testing of excess blood samples identified 204 patients with undocumented HCV infection [20]. Of those, 26 percent would have been identified by risk-based testing (eg, history of injection drug use or HIV infection), whereas an additional 49 percent would have been identified by screening based on birth between 1945 and 1965.

However, the incidence and prevalence of HCV infection among younger individuals have subsequently increased, and such patients now represent a higher relative proportion of the burden of HCV infection as adults in the 1945 to 1965 birth cohort are being identified and treated. In a study evaluating the prevalence of HCV viremia in the United States from 1999 to 2016, it decreased over time among the 1945 to 1965 birth cohort, remained stable in the 1965 to 1985 birth cohort, and increased in the after-1985 birth cohort [21]. Screening of additional high-risk birth cohorts, such as individuals 15 to 30 years old in the United States, appears cost effective [22,23].

Nevertheless, implementation of birth cohort screening has also been suboptimal [24].

**Limited potential harms** — The physical harms of HCV screening are limited to blood testing. For those in whom HCV infection is identified, treatment is well tolerated and uncommonly associated with serious adverse effects. (See "Direct-acting antivirals for the treatment of hepatitis C virus infection", section on 'Class adverse effects'.)

Other potential harms are related to the psychological effects and social stigma of an HCV diagnosis (or a false-positive HCV test). Some retrospective studies have suggested self-reported strains in relationships and negative psychological impact associated with the diagnosis [25,26]. However, these studies were performed prior to the availability of highly effective therapy for HCV infection.

### Repeat screening for select individuals

**Those with ongoing risk** — Ongoing testing for HCV infection beyond one-time screening is appropriate for patients who have risk factors that result in continued potential exposure ( algorithm 1). These include individuals with:

- Ongoing injection drug use
- Men who have sex with men (MSM) who have HIV or are on pre-exposure prophylaxis to prevent HIV
- Long-term sexual partners of individuals with HCV
- Patients who are on maintenance hemodialysis

Risk factors for HCV infection are discussed elsewhere. (See "Epidemiology and transmission of hepatitis C virus infection", section on 'Routes of transmission'.)

The frequency and method of testing for such individuals are unclear, as there are no studies evaluating the optimal interval for repeat HCV screening. Every 6 to 12 months is a reasonable interval. For pregnant women who are actively using injection drugs, we repeat screening shortly prior to delivery, even if they have been screened earlier in the pregnancy.

For patients on maintenance hemodialysis, the Kidney Disease: Improving Global Outcomes (KDIGO) HCV guidelines recommend screening every six months [27]. (See "Hepatitis C virus infection in patients on maintenance dialysis", section on 'Screening and diagnosis'.)

**Pregnant individuals** — We agree with recommendations from the CDC to screen pregnant individuals for HCV during each pregnancy, regardless of risk factors [1]. Although antiviral treatment is not administered during pregnancy because fetal safety has not been established, identifying pregnant individuals can help inform intrapartum management and facilitate follow-up for at-risk infants. This is discussed in detail elsewhere. (See "Vertical transmission of hepatitis C virus", section on 'Screening and prevention' and "Vertical transmission of hepatitis C virus", section on 'Possible risk factors for transmission'.)

**Patients with consistent clinical features** — Testing for chronic HCV infection (even if they have been screened for HCV in the past) should be performed in patients who have evidence of liver disease (eg, with abnormal aminotransferases or cirrhosis) or in those who have extrahepatic manifestations associated with HCV infection. Such extrahepatic manifestations include:

- Porphyria cutanea tarda
- Mixed cryoglobulinemia
- Lichen planus
- Necrolytic acral erythema
- Unexplained arthritis or false-positive rheumatoid factor
- Sjögren's disease/sicca symptoms
- Membranoproliferative glomerulonephritis
- Idiopathic thrombocytopenic purpura

The clinical features of chronic HCV infection are discussed in detail elsewhere. (See "Clinical manifestations and natural history of chronic hepatitis C virus infection", section on 'Clinical features' and "Extrahepatic manifestations of hepatitis C virus infection".)

**At-risk children and adolescents** — Although routine screening is not recommended for children and adolescents, HCV screening is warranted if they have exposure risk or other risk factors. This includes birth to a mother with HCV infection, injection drug use, HIV infection, and birth in a high-prevalence country. Screening in children is discussed in detail elsewhere. (See "Hepatitis C virus infection in children", section on 'Screening'.)

## DIAGNOSIS

The diagnosis of chronic HCV infection is usually made in a patient with a reactive HCV antibody test and a positive molecular test that detects the presence of HCV RNA.

### Initial testing

**Standard approach** — Initial screening or diagnostic evaluation for chronic HCV typically begins with an antibody test (ideally with a reflex HCV RNA test). Several different antibody tests are available, including laboratory-based immunoassays, rapid point-of-care tests, and home-based tests, and all can be used as the initial assay for antibody testing for HCV. (See 'Antibody testing' below.)

For most patients, a negative antibody test indicates that the patient does not have chronic HCV infection and does not warrant further evaluation. (See 'Nonreactive anti-HCV antibody' below.)

A reactive or indeterminate/equivocal antibody test should be followed by HCV RNA testing (ideally this is reflexively performed, but it has to be ordered separately in many cases). Quantitative HCV RNA tests used to confirm the diagnosis should have a detection level of 25 international units/mL or lower. (See 'HCV RNA assays' below.)

If HCV RNA is detected, the diagnosis of HCV infection is confirmed. If HCV RNA is not detected, then a reactive antibody likely represents either a past HCV infection that subsequently was cleared or a false-positive antibody test. The different testing outcomes are discussed in further detail below. (See 'Reactive antibody and positive RNA test' below and 'Reactive antibody and negative RNA test' below.)

These recommendations on testing are consistent with the joint HCV guidelines from the American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA) [28,29].

In resource-limited locations or other settings where HCV RNA testing is not accessible, HCV core antigen testing may be a more affordable alternative, if available. (See 'HCV core antigen test' below.)

**Alternative approaches for special populations**

**Very recent exposure** — For patients who have had a very recent exposure (eg, needlestick injury, recent injection drug use), acute HCV infection may be a possibility and is not well detected by screening methods for chronic HCV infection. In such cases, additional testing, including immediate and longitudinal HCV RNA and liver enzyme testing may be warranted ( algorithm 2). The diagnosis of acute HCV infection is discussed in detail elsewhere. (See "Clinical manifestations, diagnosis, and treatment of acute hepatitis C virus infection in adults", section on 'Diagnosis'.)

**Concern for false-negative antibody response** — For patients who have a greater likelihood of false-negative antibody testing (eg, patients with severely immunocompromising conditions, on hemodialysis, or with suspected acute hepatitis C infection), antibody testing and HCV RNA testing can be checked simultaneously. (See 'Nonreactive anti-HCV antibody' below.)

**Retesting a patient with known reactive HCV antibody** — Some patients who already have a reactive HCV antibody test (eg, from a prior infection that spontaneously cleared or was successfully treated) may warrant continued screening because of ongoing risk factors (see 'Those with ongoing risk' above). In such cases, an HCV RNA test is used to detect reinfection.

**Exposed infants** — For infants born to HCV-infected mothers, we typically delay antibody testing until after 18 months of age to ensure that anti-HCV antibodies detected in the child do not represent maternal antibodies that had crossed the placenta. If the child has a reactive HCV antibody test, HCV RNA testing is performed (ideally, reflexively).

If an earlier diagnosis is desired, an HCV RNA test can be performed in the first year of life. (See "Vertical transmission of hepatitis C virus", section on 'Diagnosis'.)

**Result interpretation**

**Nonreactive anti-HCV antibody** — If the antibody test is nonreactive, then chronic HCV infection is unlikely and testing can stop ( algorithm 1).

In occasional situations, however, patients may lack detectable levels of anti-HCV antibodies despite having an HCV infection, and thus testing for HCV RNA despite a nonreactive antibody test is important to exclude infection. These include severely immunocompromised patients,

patients on hemodialysis, and those who are suspected of having acute HCV infection because of symptoms or recent exposures.

- **Severely immunocompromised and hemodialysis patients** – Patients on hemodialysis, transplant recipients, and those with advanced HIV infection may have a higher rate of false-negative antibody testing than immunocompetent patients [30,31].

  Thus, we often perform HCV RNA testing to evaluate for HCV infection even if the HCV antibody test is nonreactive in such patients, particularly if the patient has an elevated transaminase level or other concern for chronic hepatitis. However, for patients who are undergoing serial screening for HCV infection (eg, patients on maintenance hemodialysis), repeatedly checking HCV RNA levels despite negative HCV antibody tests is likely not necessary in the absence of concern for recent exposure [27].

  HCV infection is diagnosed if the HCV RNA is positive, even if the HCV antibody test is nonreactive.

- **Patients with acute hepatitis or recent exposure** – In patients suspected of having acute HCV infection, either because of symptoms or signs consistent with acute hepatitis or because of a recent exposure, HCV RNA should be checked at the same time as antibody testing. Following exposure, HCV RNA becomes detectable prior to reactive antibodies. Most patients develop detectable antibodies between two and six months after exposure. Antibody testing is positive in 50 percent of patients with acute HCV infection at the time of presentation and in 90 percent at some time during the acute illness [32]. Testing for HCV RNA allows earlier diagnosis. (See "Clinical manifestations, diagnosis, and treatment of acute hepatitis C virus infection in adults".)

**Reactive antibody and positive RNA test** — A positive HCV RNA result is evidence of HCV infection ( algorithm 1). Usually, patients who have both reactive anti-HCV antibody and detectable HCV RNA have chronic infection. However, in some cases, patients acutely infected with HCV will also have a reactive antibody test and positive HCV RNA. In these cases, the distinction between acute and chronic hepatitis C is difficult and must take into account recent exposures, the presence of symptoms, prior HCV and aminotransferase testing results, and patterns of HCV RNA levels over time. This is discussed in detail elsewhere. (See "Clinical manifestations, diagnosis, and treatment of acute hepatitis C virus infection in adults", section on 'Patients with acute hepatitis'.)

For patients diagnosed with HCV infection, linking to medical care for further evaluation is important. This includes assessment of the extent of liver disease through physical exam,

laboratory testing, and any additional staging tests. (See "Patient evaluation and selection for antiviral therapy for chronic hepatitis C virus infection", section on 'Evaluation'.)

**Reactive antibody and negative RNA test** — The absence of detectable HCV RNA essentially confirms the absence of chronic HCV infection ( algorithm 1). False-negative tests for RNA are unusual when sensitive quantitative or qualitative tests with a low level of detection (eg, <25 international units/mL) are used.

In this situation, the reactive anti-HCV antibody most likely represents prior infection that subsequently cleared spontaneously (or following successful therapy) or a false-positive antibody test due to technical reasons. The estimated rate of spontaneous clearance of virus after infection is 20 to 45 percent depending upon the age and immune status of the individual at the time of infection [33]. (See "Clinical manifestations and natural history of chronic hepatitis C virus infection".)

Other, less frequent situations may result in a reactive antibody and negative RNA test:

- Detection of anti-HCV antibodies that have been passively acquired from blood transfusions. In this situation, anti-HCV disappears over the next few weeks in keeping with the half-life of immunoglobulin G (IgG). This is now extremely unusual because of improved testing of the blood supply. (See "Epidemiology and transmission of hepatitis C virus infection".)
- Detection of maternal anti-HCV antibodies in babies. (See "Vertical transmission of hepatitis C virus".)
- Recurrent episodes of viremia with genetic identity to the original infecting HCV strain have been described in injecting drug users who were thought to have cleared HCV [34]. It is unclear how frequent this phenomenon occurs.
- The amount of HCV RNA may be below the limit of detection of the assay, or there may be other technical problems with the test. This is less of an issue when currently available, sensitive, qualitative (TMA) and quantitative (real-time polymerase chain reaction [PCR]) assays are used. (See 'HCV RNA assays' below.)

## ADDITIONAL EVALUATION

The most important aspects of initial care of the patient newly diagnosed with HCV involve evaluating the extent of liver damage and determining candidacy for treatment. Selection of patients for treatment and assessment prior to treatment are discussed in more detail

elsewhere. (See "Patient evaluation and selection for antiviral therapy for chronic hepatitis C virus infection", section on 'Evaluation'.)

## DIAGNOSTIC TECHNIQUES

**Antibody testing** — Antibodies to HCV can be detected using a number of assays, including standard immunoassays that are performed in a laboratory, rapid immunoassays that can be performed at the point of care, and home tests on specimens self-collected by the patient. Once antibodies develop, they usually remain detectable, even if the patient clears HCV infection spontaneously or through treatment. Thus, a reactive antibody test alone is not sufficient to make the diagnosis of chronic HCV infection.

**Standard immunoassay testing** — The standard test used by most clinical laboratories to detect anti-HCV antibodies in serum and plasma is an immunoassay, which can be linked to various methods of signaling a positive test, including an enzymatic reaction (EIA, also called enzyme-linked immunosorbent assay or ELISA) or light emission (chemiluminescence immunoassay). These immunoassays have many advantages in the diagnostic setting, including ease of use, low variability, ease of automation, and relatively low expense.

In the United States, several US Food and Drug Administration (FDA)-approved immunoassays are available [35]; these generally detect anti-HCV antibodies by using recombinant antigens from the core and the nonstructural proteins NS3, NS4, and NS5 as targets [36-38]. These tests have sensitivity and specificity approaching 100 percent.

However, there is a delay in anti-HCV antibody generation and detection following infection. Anti-HCV antibody assays become positive as early as eight weeks after exposure, with most patients seroconverting between two and six months after exposure [39-41]. Immunocompromised individuals with HCV infection, including those with HIV infection, patients on dialysis, and transplant recipients, may not generate sufficient levels of anti-HCV antibodies for detection [30,42,43]. Thus, for immunocompromised patients and for patients with suspected acute HCV infection, HCV RNA testing should be considered even if anti-HCV tests are negative. (See 'Nonreactive anti-HCV antibody' above.)

In certain parts of the world, there may be other, specific issues that interfere with the accuracy of HCV immunoassays. In a study of 1000 individuals in Uganda who had not been previously treated for HCV infection, the prevalence of anti-HCV positivity by EIA was 7.6 percent, but HCV RNA was not detected in any of those cases [44]. A reactive anti-HCV EIA was associated with a

reactive *Schistosoma* EIA, suggesting the possibility of cross-reactivity; however, the study was not able to distinguish cleared infection from false EIA positivity.

Laboratory-based immunoassays are typically performed on plasma or serum. In resource-limited settings, a potential alternative is obtaining a dried blood spot of capillary blood by fingerstick to be sent to a laboratory with high throughput immunoassay testing. In a pooled quantitative meta-analysis of 19 studies, the sensitivity and specificity were 98 and 99 percent, respectively, compared with testing on venous blood samples [45].

**Other antibody tests**

- **Rapid, point-of-care tests** – Several rapid tests for HCV antibodies have been developed that have performance comparable to standard laboratory-based immunoassays. These tests can be run on venous blood, fingerstick blood, serum, plasma, and oral fluid, and results are generally available in less than 30 minutes. The tests are designed for point-of-care testing to provide increased opportunities for HCV testing outside of traditional clinical settings [46]. In a meta-analysis that included 18 trials, point-of-care tests on whole blood or fingersticks had pooled sensitivities of 98.9 percent (95% CI 94.5-99.8) and specificities of 99.5 percent (95% CI 97.5-99.9) for diagnosing HCV infection as compared with immunoassay detection [47]. However, certain tests perform better than others [48].

- **Self-collected tests** – Several over-the-counter antibody testing kits are commercially available in the United States and elsewhere. For many of these, the patient collects a blood sample with a finger stick and sends the specimen to a laboratory. Analytic performance of these assays is uncertain.

- **Recombinant immunoblot assay** – The recombinant immunoblot assay (RIBA) is a test that detects HCV antibodies with similar sensitivity but higher specificity than screening second-generation immunoassays. It is no longer available in the United States but may be available in other parts of the world and has been used in earlier studies to determine the performance of immunoassays.

  In locations where the RIBA remains available, it can help distinguish between past infection (RIBA positive) and false-positive antibody testing (RIBA negative) in individuals who have a reactive immunoassay and a negative HCV RNA test. RIBA can also be interpreted as indeterminate, in which case, other testing must be done to make the distinction. (See 'Reactive antibody and negative RNA test' above.)

**HCV RNA assays** — HCV RNA detection and quantification are essential tools in the diagnosis and management of individuals with chronic HCV infection. HCV RNA assays are used to confirm

the presence or absence of infection and to quantify the amount of HCV RNA present.

Nucleic acid tests (NATs) for detection of HCV RNA have been traditionally divided into two categories: qualitative and quantitative assays:

- **Quantitative tests** – These assess the quantity of HCV RNA in international units/mL and are used to detect infection, to measure baseline HCV viral load prior to treatment, and to assess response to therapy. Outside of the context of treatment, serial HCV RNA measurements in those with chronic infection are not needed since the viral load does not have prognostic value.

  Contemporary assays are highly sensitive, with lower limits of detection (LLOD) of approximately 10 to 15 international units /mL, and have a wide dynamic range (7 to 8 log[10] international units/mL). In addition to the LLOD (the lowest viral level that can be detected), quantitative assays have a lower limit of quantification (LLOQ, the lowest viral level that can be quantified). The LLOD does not always correspond to the LLOQ for a given test, and thus a viral level may be unquantifiable but detected [49]. Most patients with chronic HCV infection have HCV RNA levels much greater than the lower level of detection of quantitative tests.

  All HCV RNA assays are calibrated using the World Health Organization (WHO) HCV international unit standard to provide better accuracy and comparability of results across different assays. The standard is based upon the quantitative analysis of HCV RNA genotype 1. Results can vary between assays, especially for some non-1 HCV genotype specimens [50,51]. As a result, serial measurements of HCV RNA during treatment should ideally be performed using the same assay throughout.

- **Qualitative tests** – They provide results as either positive or negative and are used to detect infection and assess response to therapy. Qualitative tests are capable of detecting low levels of HCV RNA; some have a lower limit of detection as low as <10 international units/mL HCV RNA.

In the United States, FDA-approved HCV RNA tests generally use real-time polymerase chain reaction (PCR) or transcription-mediated amplification (TMA) to amplify and quantify viral RNA. Some are able to simultaneously detect other viral pathogens (ie, HIV and hepatitis B virus).

HCV RNA detection methods are traditionally performed on serum or plasma samples. Testing of dried blood spots prepared from a whole-blood specimen obtained by fingerstick also appears relatively accurate, with a lower detection limit as low as 250 to 500 international units/mL in some cases, and could be a useful tool in resource-limited settings [52,53].

**HCV core antigen test** — Several immunoassays have been developed to detect the HCV core (HCV cAg) protein, a component of the viral particle [54,55]. In resource-limited settings where NAT is not available, WHO guidelines recommend that an HCV cAg test be used instead to confirm viremia [3]. This test is not available in certain resource-rich settings, including the United States.

In a systematic review of studies evaluating the accuracy of such tests, the most studied assays (Abbott ARCHITECT HCV Ag assay and the Ortho HCV Ag ELISA) had good performance, with pooled sensitivities and specificities for detecting HCV viremia of approximately 93 and 99 percent, respectively [54]. The ARCHITECT HCV Ag assay performed well in identifying infected individuals with HCV RNA level >3000 international units/mL. The Hunan Jynda Bioengineering Group HCV Ag ELISA assay had poor performance.

There are limited data on performance of these tests in individuals with HIV or hepatitis B virus coinfection and with genotypes 4, 5, and 6 HCV infection.

## BLOOD DONOR SCREENING

Volunteer blood donors are initially screened for risk factors through a questionnaire. Donated blood is then screened for HCV using ELISA for anti-HCV antibodies. In addition, pooled samples of donated blood or blood products are screened with nucleic acid testing (NAT), an ultrasensitive amplification-based technique to detect HCV RNA. If a pool tests positive, then the individual donor units are tested. This identifies donors who are HCV infected but anti-HCV negative, such as those with acute HCV infection. Only seronegative and NAT negative units are released [56].

## SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Hepatitis C virus infection".)

## INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5$^{th}$ to 6$^{th}$ grade reading level, and they answer the four or five key questions a patient might have about a given

condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topic (see "Patient education: Hepatitis C (The Basics)")
- Beyond the Basics topic (see "Patient education: Hepatitis C (Beyond the Basics)")

## SUMMARY AND RECOMMENDATIONS

- **Rationale** – Hepatitis C virus (HCV) infection is a global health problem that can progress to cirrhosis and end-stage liver disease in a substantial proportion of patients. Because it is frequently asymptomatic, screening is essential to improving detection and ultimately treatment of infected individuals. (See 'Rationale' above.)
- **Universal one-time screening** – We suggest one-time screening for HCV infection in all adults ≥18 years of age rather than selective screening (**Grade 2C**). This recommendation is supported by the substantial individual benefit of treatment of HCV infection, the minimal harms of screening, and the limitations of risk-based screening in identifying patients with infection. (See 'Routine one-time screening for adults' above.)
- **Selective repeat screening** – Repeat screening is warranted for patients who have ongoing risk of exposure (eg, people who use injection drugs, patients on chronic hemodialysis, men who have sex with men who have HIV or are using pre-exposure prophylaxis to prevent HIV, and long-term sex partners of individuals with HCV infection) and for pregnant individuals during each pregnancy. (See 'Repeat screening for select individuals' above.)
- **Testing for clinical suspicion** – Testing for HCV infection is also warranted in people with evidence of liver disease, with extrahepatic conditions associated with HCV (eg, porphyria cutanea tarda, mixed cryoglobulinemia), or with known exposure. (See 'Patients with consistent clinical features' above and 'Very recent exposure' above.)

- **Diagnosis** – The diagnosis of chronic HCV infection is usually made in a patient with a reactive HCV antibody test and a positive molecular test that detects the presence of HCV RNA ( algorithm 1). Usually, patients who have both reactive anti-HCV antibody and detectable HCV RNA have chronic infection, although these may also be seen in some acutely infected patients. (See 'Diagnosis' above.)

  - **Initial antibody test** – Initial screening or diagnostic testing for chronic HCV typically begins with an antibody test (ideally with a reflex HCV RNA test). (See 'Standard approach' above.)

  - **Nonreactive antibody test** – For most people, chronic HCV infection is unlikely with a nonreactive antibody test, and testing can stop. Patients who are on hemodialysis, are severely immunocompromised, or are suspected of having an acute HCV infection may not have detectable anti-HCV antibodies despite the presence of infection; in such patients, HCV RNA testing despite a nonreactive antibody test is important to exclude infection. (See 'Nonreactive anti-HCV antibody' above.)

  - **Reactive antibody test** – This should be followed with an HCV RNA test. The absence of detectable HCV RNA using a sensitive assay essentially confirms the absence of chronic HCV infection. False-negative tests for RNA are unusual. A reactive antibody test in this setting is generally a false positive or reflective of past, cleared infection. A positive HCV RNA result is evidence of HCV infection. (See 'Reactive antibody and negative RNA test' above and 'Reactive antibody and positive RNA test' above.)

  A diagnostic approach to suspected acute hepatitis C is presented separately. (See "Clinical manifestations, diagnosis, and treatment of acute hepatitis C virus infection in adults", section on 'Diagnosis'.)

- **Diagnostic techniques** – Antibodies to HCV can be detected using a number of assays, including standard immunoassays that are performed in a laboratory, rapid immunoassays that can be performed at the point of care, and home tests on specimens self-collected by the patient. Nucleic acid tests for detection of HCV RNA have been traditionally divided into two categories: qualitative and quantitative assays. Most currently available quantitative tests have a lower level of detection that is comparable to qualitative tests. (See 'Diagnostic techniques' above.)

- **Postdiagnostic evaluation** – Important aspects of initial care of the patient newly diagnosed with HCV involve evaluating the extent of liver damage and assessing factors that inform treatment decisions. These are discussed in detail elsewhere. (See "Patient

evaluation and selection for antiviral therapy for chronic hepatitis C virus infection", section on 'Evaluation'.)

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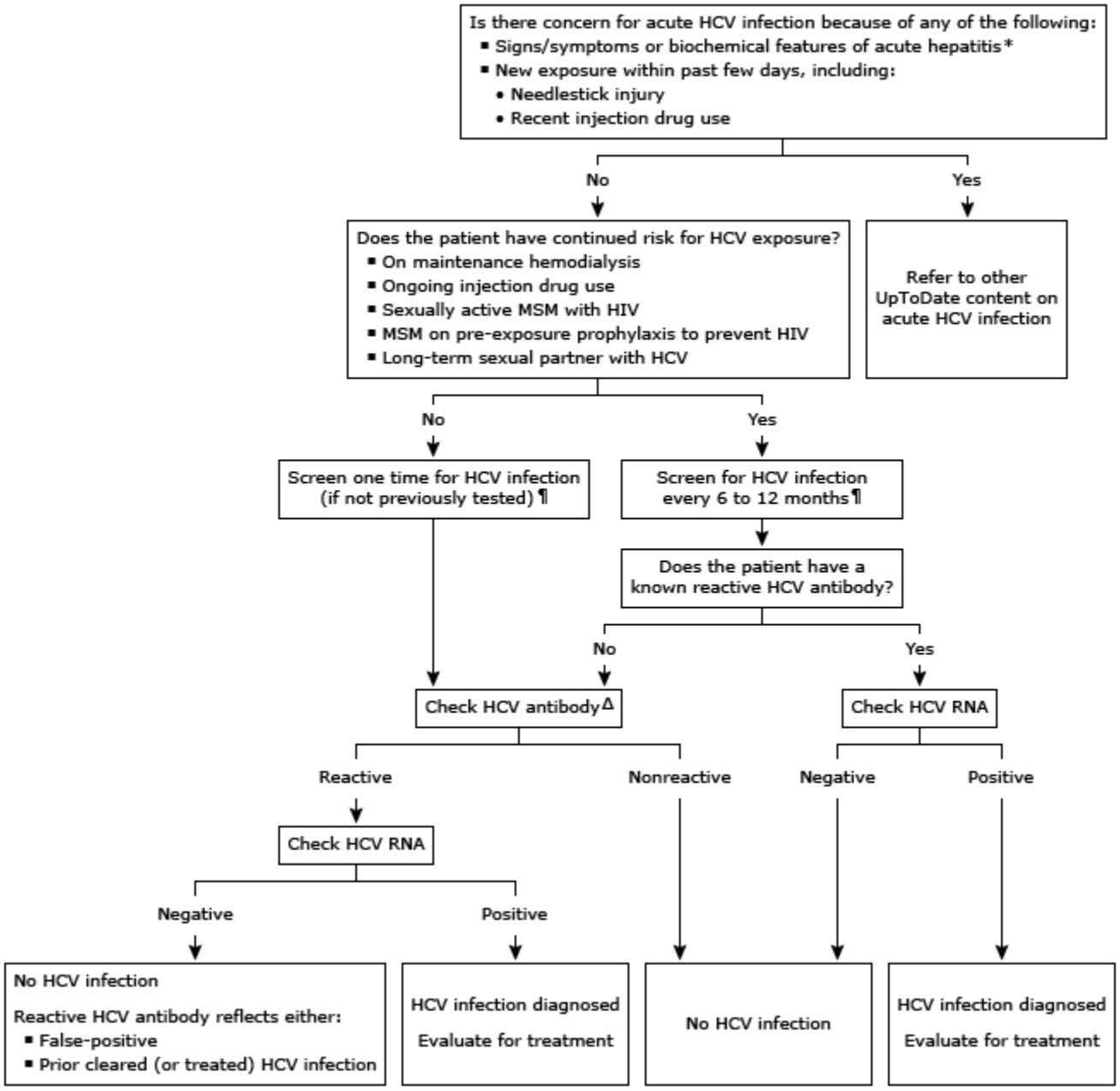
Topic 89950 Version 36.0

## GRAPHICS

### Screening and diagnosis of chronic hepatitis C infection in adults aged ≥18 years




We suggest at least one-time screening for chronic HCV infection in all adults ≥18 years. Patients with ongoing risk for exposure warrant repeat screening.

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HCV: hepatitis C virus; MSM: men who have sex with men; RNA: ribonucleic acid.

* These include new-onset jaundice and markedly elevated transaminases.

¶ For pregnant individuals, we suggest screening during each pregnancy, regardless of risk factors. For pregnant individuals who are actively using injection drugs, we repeat screening shortly prior to

delivery, even if they have been screened earlier in the pregnancy.

Δ For patients on hemodialysis or with a severely immunocompromising condition (eg, advanced HIV, organ transplantation), HCV RNA can be checked at the same time as HCV antibody testing because of concern for a false-negative antibody. In such cases, a positive HCV RNA confirms the diagnosis of HCV infection, whereas a negative HCV RNA rejects it.

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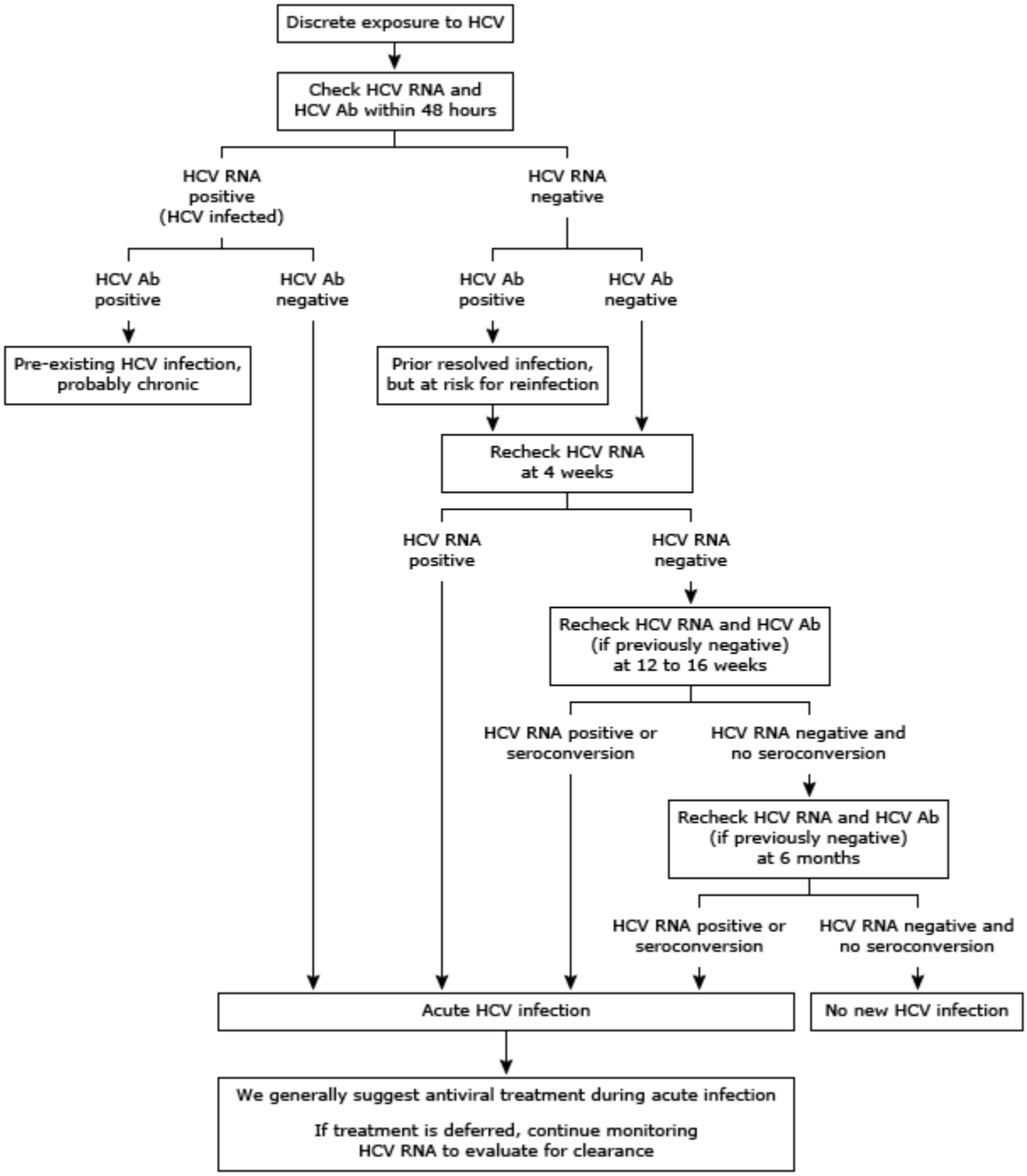
Graphic 127067 Version 4.0

## Evaluation for acute HCV in a patient with recent exposure




This algorithm represents one approach to the diagnosis of acute HCV infection following a known exposure to HCV. After evaluating the baseline HCV RNA and antibody levels, repeat testing intervals over the next six months depend, in part, on how soon detection of infection is desired. Aminotransferases can also be checked as well, and new elevations in these levels would be a trigger to recheck HCV RNA sooner if not already detectable.

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HCV: hepatitis C virus; Ab: antibody.

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Graphic 101864 Version 3.0

## Contributor Disclosures

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