INTRODUCTION — Hepatitis C virus (HCV) can cause both acute and chronic hepatitis. The acute process is self-limited, rarely causes hepatic failure, and usually leads to chronic infection. Chronic HCV infection often follows a progressive course over many years and can ultimately result in cirrhosis, hepatocellular carcinoma, and the need for liver transplantation. (See "Clinical manifestations and natural history of chronic hepatitis C virus infection".)

This topic will provide a general overview of the issues involved with the treatment of chronic HCV. Patient selection for treatment, specific treatment regimens, and the management of treatment induced side effects are discussed in detail elsewhere. (See "Patient evaluation and selection for antiviral therapy for chronic hepatitis C virus infection" and "Treatment regimens for chronic hepatitis C virus genotype 1" and "Treatment regimens for chronic hepatitis C virus genotypes 2 and 3" and "Treatment regimens for chronic hepatitis C virus genotypes 4, 5, and 6" and "Direct-acting antivirals for the treatment of hepatitis C virus infection" and "Management of the side effects of peginterferon and ribavirin used for treatment of chronic hepatitis C virus infection".)

GUIDELINES — Guidelines for the diagnosis and management of HCV infection were released jointly by the American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA) in 2014 and can be accessed at www.hcvguidelines.org [1]. The discussion in this topic is generally consistent with those guidelines.

Other guidelines include treatment recommendations from the European Association for the Study of the Liver (EASL), which was published in 2014 [2], and United Kingdom consensus guidelines, which were updated in 2014 [3]. World Health Organization (WHO) also released guidelines in 2014 on screening and treatment of HCV, intended primarily for clinicians and policy-makers in low- and middle-income countries [4].
GENERAL MANAGEMENT — Antiviral therapy is the cornerstone of treatment of chronic hepatitis C virus (HCV) infection. With current antiviral therapies, HCV is relatively easily treated and can be eliminated in almost all patients. Other general measures in the management of patients with chronic HCV include psychologic counseling, symptom management, dose adjustment of medications, assessment of fibrosis, and screening for complications of cirrhosis if present.

Additional testing — Patients diagnosed with HCV should also be tested for HIV and hepatitis B due to the common modes of transmission. In addition, they should be tested for antibodies to hepatitis A and B viruses to determine if vaccination is required. (See "Screening and diagnostic testing for HIV infection" and "Diagnosis of hepatitis B virus infection" and "Immunizations for patients with chronic liver disease".)

Counseling — Although most patients with chronic HCV infection are asymptomatic at the time of diagnosis, they are faced with a significant threat to their health, which can have important emotional and physical consequences. Counseling and screening for depression should be a major consideration, both at diagnosis and during subsequent follow-up. Many patients benefit from participation in a support group. (See "Patient information: Hepatitis C (Beyond the Basics)".)

Counseling should include discussions about the routes of HCV transmission, as most patients are concerned about sexual transmission and the risk of infecting household contacts (table 1). In addition, patients should be informed that obesity, cigarette smoking, and marijuana smoking can promote hepatic fibrosis [5-8]. Weight loss should be attempted if obesity is present, and patients who smoke cigarettes or marijuana should be offered assistance with quitting. (See "Epidemiology and transmission of hepatitis C virus infection" and "Obesity in adults: Overview of management" and "Overview of smoking cessation management in adults" and "Cannabis use disorder: Treatment, prognosis, and long-term medical effects".)

Diet — Many patients are concerned about dietary factors that could favorably or adversely affect the disease. Although no particular diet has been shown to be beneficial in patients with chronic HCV infection, alcohol promotes the progression of chronic HCV. As a result, we recommend abstinence. (See "Hepatitis C and alcohol", section on 'How much alcohol is too much?'.)

Coffee consumption (more than two cups per day) has been associated with a reduced risk of hospitalization and mortality from a number of chronic liver diseases including chronic viral hepatitis, nonalcoholic steatohepatitis (NASH), and alcoholic liver disease [9,10]. In addition, high levels of coffee consumption appear to increase sustained virologic responses in those receiving peginterferon and ribavirin. However, these observations may not
necessarily justify recommending increased consumption of coffee. (See "Predictors of a sustained virologic response following treatment with peginterferon and ribavirin for chronic hepatitis C virus infection", section on 'Other predictors'.)

**Fatigue** — Many patients with HCV complain of fatigue. The cause of the fatigue is uncertain and may be difficult to ascribe to liver disease alone rather than another illness such as depression. Fatigue improves in some patients who have a sustained virologic response following interferon-based therapy. One of the largest series addressing this issue included 431 patients who underwent treatment for HCV. Fatigue improved significantly more often in responders than in nonresponders (35 versus 22 percent) [11]. Subsequently, a number of studies with all-oral antiviral therapies have shown improvements in patient related outcomes associated with viral clearance during or after the treatment regimen [12,13]. (See "Patient evaluation and selection for antiviral therapy for chronic hepatitis C virus infection", section on 'Symptom alleviation'.)

**Ondansetron** (a 5-HT3 receptor antagonist, 4 mg twice daily) significantly improved fatigue in a placebo-controlled trial involving 36 patients [14]. The rationale for its use was based upon the observation that serotonin is associated with fatigue in animal and human models [15]. However, long-term efficacy is unclear, and treatment may be associated with constipation and cardiac arrhythmias.

**Dose adjustments of medications** — Prescription and over-the-counter medications usually do not require a dose adjustment in patients who have normal hepatic function. However, nonsteroidal anti-inflammatory drugs can be hepatotoxic and should be avoided in patients with advanced liver disease. (See "Drugs and the liver: Metabolism and mechanisms of injury").

Many patients voice concern about taking acetaminophen due to its association with liver injury when taken in high doses. Patients do not need to avoid acetaminophen, but we suggest that the dose of acetaminophen not exceed 2 g per 24 hours. (See "Acetaminophen (paracetamol) poisoning in adults: Pathophysiology, presentation, and diagnosis").

While statins are frequently withheld from patients with chronic liver disease, available data fail to show an increased risk of adverse effects in patients with compensated chronic liver disease, suggesting that statin use is safe in patients with stable HCV infection [16,17]. In addition, there are some data that suggest statin use is associated with a reduction in portal pressure in patients with cirrhosis [18].
Screening for esophageal varices and hepatocellular carcinoma — Patients with cirrhosis should be screened for the presence of esophageal varices by upper endoscopy. Patients with cirrhosis should undergo surveillance for hepatocellular carcinoma (HCC) because HCC occurs at a rate of 1 to 4 percent per year. (See "Clinical features and diagnosis of primary hepatocellular carcinoma", section on 'Screening and surveillance' and "Cirrhosis in adults: Overview of complications, general management, and prognosis", section on 'Preventing and identifying complications'.)

Vaccination — Recommendations for the vaccination of patients with chronic HCV are presented separately. (See "Immunizations for patients with chronic liver disease".)

GOAL OF ANTIVIRAL THERAPY — The goal of antiviral therapy in patients with chronic HCV is to eradicate HCV RNA, which is predicted by attainment of a sustained virologic response (SVR). An SVR is associated with a 97 to 100 percent chance of being HCV RNA negative during long-term follow-up and can therefore be considered cure of the HCV infection [19-22]. Attaining an SVR has been associated with decreases in all-cause mortality, liver-related death, need for liver transplantation, hepatocellular carcinoma rates, and liver-related complications, even among those patients with advanced liver fibrosis [20,23-31]. (See "Patient evaluation and selection for antiviral therapy for chronic hepatitis C virus infection", section on 'Rationale for treatment'.)

PATIENT SELECTION FOR ANTIVIRAL THERAPY — All patients with virologic evidence of chronic HCV infection (ie, detectable HCV viral level over a six month period) should be considered for treatment. With the availability of direct acting antivirals, highly effective, all-oral regimens are a possibility for the vast majority of HCV infected patients who have access to these agents. The evaluation and selection of patients for antiviral therapy is discussed in detail elsewhere. (See "Patient evaluation and selection for antiviral therapy for chronic hepatitis C virus infection".)

Additional considerations should be taken into account for certain populations, such as those with chronic kidney disease or history of liver transplantation. These are discussed in detail elsewhere. (See “Treatment of chronic hepatitis C infection in adults with renal impairment” and "Liver transplantation for hepatitis C virus infection".)

TREATMENT OPTIONS — Antiviral therapy of HCV has been rapidly evolving with the introduction and development of direct-acting antivirals that offer the potential for highly effective, interferon-free (and in some cases, interferon- and ribavirin-free) regimens for the majority of HCV infected individuals. Treatment selection varies by genotype and other patient factors. This is discussed in detail elsewhere:
In the United States, the high prices of these all-oral antiviral regimens have garnered substantial attention among medical and lay communities. Several studies have suggested that these regimens, even at their introductory high cost, are cost-effective for many populations, including those with genotype 1 infection or advanced fibrosis, because of their superior efficacy in clinical trials [32-36]. If these new agents could be made more affordable to patient and third party payers, more patients could be successfully treated with them.

**ASSESSING A TREATMENT RESPONSE** — Virologic response to treatment should be assessed by checking the viral load at 12 weeks following the cessation of therapy. Although a sustained virologic response (SVR) was traditionally defined as an undetectable viral level at 24 weeks post-treatment, an undetectable level at 12 weeks post-treatment is generally maintained through week 24.

**SIDE EFFECTS OF TREATMENT** — Direct acting antivirals (DAAs) are generally well tolerated. Specific side effects are discussed in detail elsewhere. (See "Direct-acting antivirals for the treatment of hepatitis C virus infection").

For patients who are treated with a regimen that contains peginterferon and ribavirin, side effects can be more substantial. These most commonly are flu-like symptoms, fatigue, neuropsychiatric symptoms, and hematologic effects. (See "Management of the side effects of peginterferon and ribavirin used for treatment of chronic hepatitis C virus infection").

Care of patients with chronic HCV depends upon recognition of those at increased risk for side effects, anticipation (and prevention) of side effects, and appropriate response when they occur. Furthermore, the ability to achieve a sustained virologic response to therapy depends in part upon the degree of adherence with therapy, which may be affected by the adverse effect profile.

**TREATMENT OF EXTRAHEPATIC MANIFESTATIONS** — Chronic HCV is associated with extrahepatic manifestations such as cryoglobulinemia, porphyria cutanea tarda, and autoimmune disorders. (See "Extrahepatic manifestations of hepatitis C virus infection" and "Extrahepatic manifestations of hepatitis C virus infection", section on 'Porphyria cutanea tarda'.)
Some of the manifestations that may respond to treatment for HCV include:

- Cryoglobulinemia
- Porphyria cutanea tarda
- Leukocytoclastic vasculitis
- Necrolytic acral erythema
- Glomerulonephritis

**NOVEL/INVESTIGATIONAL TREATMENTS** — There are several safe and effective all-oral direct-acting antiviral regimens available internationally. A number of new therapies for chronic HCV are under development. The goals of future therapies will be to be pan-genotypic, of shorter duration than 12 weeks, **ribavirin**-free, less costly, and well-tolerated in special populations. Regimens in development include second-generation NS3/4 protease inhibitors and NS5A inhibitors as well as new NS5B nucleoside and non-nucleoside polymerase inhibitors.

Investigational therapies for chronic HCV infection are discussed in detail elsewhere. (See "**Investigational therapies for 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 5th to 6th 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 topics** (see "**Patient information: Hepatitis C (The Basics)**" and "**Patient information: Treatment for hepatitis C (The Basics)**")
- **Beyond the Basics topic** (see "**Patient information: Hepatitis C (Beyond the Basics)**")
SUMMARY AND RECOMMENDATIONS

- In addition to antiviral therapy, considerations in the treatment of patients with chronic hepatitis C virus (HCV) include psychologic counseling, alcohol avoidance, symptom control, dose adjustment of medications, assessment of fibrosis, and screening for complications of cirrhosis if present. (See 'General management' above.)
- The goal of treatment in patients with chronic HCV is to eradicate HCV RNA, which is associated with decreases in all-cause mortality, liver-related death, need for liver transplantation, hepatocellular carcinoma rates, and liver-related complications. (See 'Goal of antiviral therapy' above.)
- Antiviral therapy of HCV has been rapidly evolving with the introduction and development of direct-acting antivirals that offer the potential for highly effective, interferon-free (and in some cases, interferon- and ribavirin-free) regimens for the majority of HCV infected individuals. Treatment selection varies by genotype and other patient factors. (See "Treatment regimens for chronic hepatitis C virus genotype 1", "Treatment regimens for chronic hepatitis C virus genotypes 2 and 3", and "Treatment regimens for chronic hepatitis C virus genotypes 4, 5, and 6".)

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REFERENCES


# Counseling to avoid transmission of hepatitis C virus

HCV-infected persons should be counseled to avoid sharing toothbrushes and dental or shaving equipment and be cautioned to cover any bleeding wound in order to keep their blood away from others.

Persons should be counseled to stop using illicit drugs. Those who continue to inject drugs should be counseled to avoid reusing or sharing syringes, needles, water, and cotton or other paraphernalia; to clean the injection site with a new alcohol swab; and to dispose safely of syringes and needles after one use.

HCV-infected persons should be counseled that the risk of sexual transmission is low and that the infection itself is not a reason to change sexual practices (ie, those in long-term relationships need not start using barrier precautions and others should always practice "safer" sex).

HCV-infected persons should be advised to not donate blood, body organs, other tissues, or semen.

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INTRODUCTION — Diagnostic tests for hepatitis C virus (HCV) can be divided into two broad categories:

- Serologic assays that detect antibodies to hepatitis C
- Molecular assays that detect or quantify HCV RNA

Other investigations such as genotype testing, serum fibrosis panels and liver biopsy may help to predict the response to treatment and prognosis.

This topic will review the approach to diagnostic testing and evaluation of chronic HCV infection.

Recommendations on screening and other issues related to chronic HCV infection are discussed elsewhere. (See "Epidemiology and transmission of hepatitis C virus infection" and "Screening for chronic 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 in adults", section on 'Diagnosis'.)

WHOM TO TEST — Testing for chronic HCV infection is generally performed in patients who have evidence of liver disease through abnormal aminotransferases or other clinical findings or in those who have extrahepatic manifestations associated with HCV infection (such as mixed cryoglobulinemia or porphyria cutanea tarda) (table 1). Additionally, screening for chronic HCV infection is recommended for certain patients regardless of
clinical findings if they have an individual risk factor for exposure or belong to certain demographic groups that have a high-prevalence of infection, including those born between 1945 and 1965. This is discussed in detail elsewhere. (See "Screening for chronic hepatitis C virus infection".)

**DIAGNOSIS AND TESTING APPROACH** — 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.

**Testing algorithm** — Initial diagnostic evaluation for chronic HCV typically begins with an antibody test. A reactive or indeterminate/equivocal antibody test should be followed by HCV RNA testing. For patients who have a greater likelihood of false negative antibody testing (eg, immunocompromised patients or those suspected of having acute hepatitis C), HCV RNA testing should be sent at the same time as antibody testing when there is a high level of suspicion for infection.

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 'Nonreactive anti-HCV antibody' below and 'Reactive antibody and positive RNA test' below and 'Reactive antibody and negative RNA test' below.)

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.)

Most currently available quantitative tests of HCV RNA have a lower limit of detection <50 international units/mL and can be used for diagnosis of HCV. If the available quantitative test does not have that level of sensitivity, then a qualitative test should be used for diagnosis. (See 'HCV RNA assays' below.)

These recommendations are consistent with the American Association for the Study of Liver Diseases 2009 guidelines [1] and the United States Centers for Disease Control and Prevention 2013 recommendations [2] for testing and diagnosis of HCV infection.

**Nonreactive anti-HCV antibody** — If the antibody test is nonreactive, then chronic HCV infection is unlikely and testing can stop.
In occasional situations, however, patients may lack detectable levels of anti-HCV antibodies despite having a HCV infection, and thus testing for HCV RNA despite a nonreactive antibody test is important to exclude infection. These include immunocompromised patients and those who are suspected of having acute HCV infection because of symptoms or recent exposures.

**Immunocompromised 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 [3,4]. Thus, HCV RNA testing should be performed in all patients who are immunocompromised and antibody nonreactive if there is clinical suspicion of infection (eg, if there is unexplained liver disease).

**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 [5]. Testing for HCV RNA allows earlier diagnosis, which may be important since therapy during acute infection is associated with high rates of viral clearance. (See "Clinical manifestations, diagnosis, and treatment of acute hepatitis C in adults".)

**Reactive antibody and positive RNA test** — A positive HCV RNA result is evidence of HCV infection. 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 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 consideration of liver biopsy. Additionally, HCV RNA quantification (if diagnosis was made with a qualitative RNA test) and HCV genotype testing are important for patients in whom treatment is being considered. (See 'Additional evaluation' below.)

**Reactive antibody and negative RNA test** — The absence of detectable HCV RNA essentially confirms the absence of chronic HCV infection. False negative tests for RNA are unusual when sensitive quantitative or qualitative tests with a low level of detection (eg, <50 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 [6]. (See "Clinical manifestations and natural history of chronic hepatitis C virus infection".)

If the distinction between these two possibilities needs to be made, a different antibody test can be performed [2]. A nonreactive second antibody test suggests that the initial test was a false-positive. Repeatedly reactive results from different antibody assays suggest a prior, cleared infection. Neither outcome is conclusive, however. As an alternative, the signal-to-cutoff (S/CO) ratio, which is generally reported in the results, can be helpful in determining if a reactive antibody test is a true positive. The S/CO ratio that predicts a >95 percent probability of true positivity varies by the specific immunoassay used (table 2). (See 'Standard immunoassay testing' below.)

Up to 90 percent of patients who have biochemical or clinical evidence of chronic liver disease and a positive antibody test have chronic HCV infection, particularly if they have risk factors for HCV infection such as a history of transfusion, injection drug use, nasal cocaine use, or other percutaneous exposures [7,8]. Such patients who are HCV RNA negative, in whom the suspicion of infection is high, should be retested for HCV RNA again in several months. Other causes of chronic liver disease should be sought in those who are repeatedly HCV RNA negative.

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 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 [9]. 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 PCR) assays are used. (See 'HCV RNA assays' below.)
DIAGNOSTIC TESTS

**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.

**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. There are several generations of immunoassay tests, which detect antibodies that target different viral antigens and vary in accuracy.

The hepatitis C virus is a small 40 to 60 nm virus with a lipid envelope and a single-stranded RNA viral genome comprising approximately 9500 nucleotides [10]. The N-terminus encodes the basic nucleocapsid (C) followed by two glycoprotein domains, the envelope (E1), and second envelope/nonstructural-1 (E2/NS1) regions. Downstream to this region are the genes encoding nonstructural proteins NS2, NS3, NS4, and NS5, respectively. (See "Characteristics of the hepatitis C virus").

The latest, third generation EIAs (EIA-3) generally detect antibodies to recombinant antigens from the core, NS3, NS4, and NS5 proteins. These tests have very high sensitivity and high specificity [11-15]. Anti-HCV EIA tests become positive as early as eight weeks after exposure, with most patients seroconverting between two and six months after exposure [16-18]. The signal-to-cutoff (S/CO) ratio that predicts a >95 percent probability of true positivity varies by the specific immunoassay used (table 2). In a systematic review of studies that evaluated the accuracy of EIA-3 using detection of HCV RNA as a reference, the pooled sensitivity was 97.2 percent (95% CI 92-99) among 143 patients with evidence of hepatitis and 98.9 percent (CI 94-10) on a panel of 90 serum samples [13]. Specificity was 100 percent among 84 patients with either evidence of hepatitis or undergoing hemodialysis. Compared to earlier generation tests, the EIA-3 has slightly better specificity in the blood donor population [14,19]. As an example, in a study of 2620 donor blood samples that were repeatedly reactive with a third generation EIA assay at a specific signal level, the sensitivity and specificity was 89 and 93 percent, respectively, compared to an immunoblot assay. (See 'Recombinant immunoblot assay' below.)
However, in certain parts of the world, third generation EIAs may be associated with a high rate of false positivity. In a study of 1000 individuals in Uganda who had not been previously treated for HCV infection, the prevalence of anti-HCV positivity by third generation EIA was 7.6 percent, but HCV RNA was not detected in any of those cases [20]. A reactive anti-HCV EIA was associated with a reactive Schistosoma EIA, suggesting the possibility of cross-reactivity, but the study was not able to distinguish cleared infection from false EIA positivity.

Chemiluminescence immunoassays are becoming widely used, especially in clinical laboratories with high volumes. Their performance is comparable to third generation EIAs, and may even offer slightly improved specificity in the general population [21,22].

The second generation version of the EIA test, EIA-2, detects antibodies to recombinant antigens from the core (C22) and nonstructural regions 3 (C33) and 4 (C100) of HCV. Although now used less frequently than later generation assays, EIA-2 is still available. It is not quite as sensitive and specific as later generation tests. Overall, EIA-2 testing allows detection of anti-HCV in about 95 percent of individuals with HCV as confirmed by highly sensitive molecular tests such as the polymerase chain reaction (PCR) [23] or transcription-mediated amplification (TMA) [24]. The positive predictive value of the EIA-2 is lower (50 to 61 percent) in lower prevalence populations such as blood donors. The mean time to seroconversion with EIA-2 after blood transfusion is 10 weeks [11]. (See "Clinical manifestations and natural history of chronic hepatitis C virus infection".)

For immunocompromised individuals, including those with HIV infection, patients on dialysis, and transplant recipients, anti-HCV may not be detectable despite the presence of HCV infection, particularly when earlier generation EIA tests are used. Additionally, patients with acute HCV infection may not yet have developed anti-HCV antibodies. For these patients at risk for HCV infection or in whom HCV is suspected (such as those with an elevated serum ALT level), HCV RNA testing should be considered even if anti-HCV tests are negative [3,25,26]. (See 'Immunocompromised patients' above and 'Patients with acute hepatitis or recent exposure' above.)

**Rapid immunoassay 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, finger stick 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 [27].

In the United States, one rapid test (OraQuick HCV Rapid Antibody Test, OraSure Technologies, Inc, Bethlehem, PA) has been approved by the Food and Drug Administration. Although the test can be performed on various patient specimens, tests run on venous blood and finger stick blood have been
approved for use in facilities that can perform Clinical Laboratory Improvement Amendments of 1988 (CLIA)-waived tests, such as outreach clinics, community-based organizations, and clinician offices. The test is performed on a test strip and does not require additional equipment. Data suggest that the sensitivity and specificity of the test are equivalent to EIA testing [28]. In a study of over 2000 patients with risk factors for HCV infection, the OraQuick rapid test on blood derived specimens (serum, plasma, venous blood, or fingerstick) had a sensitivity of 99.7 to 99.9 percent (95% CI 99 to 100) and specificity of 99.9 percent (95% CI 99.5 to 100). Sensitivity was slightly lower for oral fluid, at 98.1 percent (95% CI 96.9 to 99) [29]. Consumption of tobacco and most types of food and drink do not affect specificity or sensitivity with a minimum wait time of five minutes. However, a low rate of false positive results were observed when testing was performed five minutes following the use of mouthwash, tooth whitening or brushing, and consumption of soda, but these was corrected by extending the wait times prior to testing.

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 to 99.8) and specificities of 99.5 percent (97.5 to 99.9) for diagnosing HCV infection as compared with immunoassay detection [30]. However, certain tests perform better than others. As an example, in one study, 1100 specimens from patients with a history of injection drug use were tested with the OraQuick test, the Multiplo Rapid HIV/HCV Antibody Test (MedMira, Inc, Halifax, Nova Scotia) and the Chembio Dual Path Platform (DPP) HCV Test (Chembio Diagnostic Systems, Inc, Medford, NY) [31]. The differences in sensitivities between the OraQuick (98 to 99 percent), Multiplo (87 to 88 percent), and Chembio (96 to 98 percent) tests were all statistically significant. There were no differences among the three tests with regard to specificity (all were greater than 99 percent specific).

**Self-collected tests** — An over-the-counter antibody testing kit ("Hepatitis C Check" [Home Access Health Corp.]) has been approved by the FDA. A sample is sent to the laboratory and results are returned within 4 to 10 business days. Data presented to the FDA suggest that the accuracy of the test is comparable to hospital laboratory-based antibody testing. The manufacturer provides a telemedicine service offering education, counseling, and clinician referral.

**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 at specific time points during therapy to guide decisions regarding duration of treatment.

Nucleic acid tests (NAT) 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. Thus, quantitative tests can be used for detection of infection. Most patients with chronic HCV infection will have HCV RNA much greater than the lower level of detection of quantitative tests. However, qualitative tests remain the gold standard for determining on-treatment viral response and confirming sustained virologic response (SVR) following successful therapy, as these are all situations in which an extremely low level of detection is critical.

All HCV RNA assays are calibrated using the World Health Organization 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 [32,33]. As a result, serial measurements of HCV RNA during treatment should ideally be performed using the same assay throughout.

**Methods of RNA detection** — Several methods can be used to detect and measure HCV RNA and have varying levels of sensitivity. These include polymerase chain reaction (PCR) based methods, transcription mediated amplification (TMA), and branched DNA testing.

PCR-based methods, called target amplification, involve extraction of nucleic acid from the virus. The nucleic acid is then hybridized to short nucleotide primers, which are complementary to the virus sequence and amplified through controlled, repeated cycles of replication of the hybridized sequence until a quantity of DNA sufficient for detection is reached. The most sensitive standard PCR assays detect HCV RNA at concentrations of approximately 50 international units/mL of patient serum.
Real time PCR includes the use of a probe hybridized to a reporter dye that can bind to the amplified product to create a signal. By comparing the signal intensity to a standard curve of control samples of known copy level, the target HCV RNA can be quantified. Real-time PCR methods have largely replaced standard PCR methods in clinical laboratories for HCV level testing. These assays have greater sensitivity with lower detection limits of approximately 15 international units/mL and a wide linear dynamic range (7 to 8 log(10) international units/mL). In addition, since real-time PCR methods do not require specimen pre-dilution, the risk of carryover contamination (which may lead to false positive HCV RNA results) is eliminated.

TMA-based methods, like PCR, amplify target HCV RNA. The TMA-based method captures the extracted virus using magnetic microbeads and the subsequent amplification of DNA by reverse transcription occurs in an isothermal, autocatalytic fashion rather than the cycling conditions used for PCR. Like PCR, the amplified DNA is labeled with a detection probe and the amplified amount of virus determined by comparison to internal negative controls. TMA methods detect HCV RNA at concentrations of approximately 10 international units/mL.

Signal amplification technologies such as bDNA do not amplify the viral nucleic acid, but rather hybridize it to specific probes that are more easily amplified for detection [34]. The bDNA assay is technically easier, less variable, and has a lower chance of cross-contamination than standard target amplification techniques. However, signal amplification lacks the sensitivity of PCR-based methods, with a lower limit of detection of 615 international units/mL.

**Quantitative tests** — Quantitative assays assess the quantity of HCV RNA in international units/mL and vary in their limits of detection and dynamic range. In the past, these assays were less sensitive than qualitative assays and were therefore not used for detection of infection or confirmation of viral clearance. More recently, real-time PCR methods have become commercially available. These assays are more sensitive than prior quantitative assays (limits of detection of approximately 10 to 15 international units/mL) and have a wide dynamic range (7 to 8 log(10) international units/mL). Thus, the real-time PCR assays offer the combined diagnostic capabilities of qualitative and quantitative assays. PCR-based methods use target amplification (see above) and bDNA methods use signal amplification.

Quantitative assays are used before treatment to measure baseline HCV viral load and during treatment to assess on-treatment response and to guide therapy (eg, stopping therapy in a patient who does not have an appropriate decline in HCV RNA during treatment). When quantitative assays are used to assess treatment response, it is important to note that the level of detection does not always correspond to the lower level of quantitation for a test, and thus a viral level may be unquantifiable but detected [35]. (See "Treatment regimens for chronic hepatitis C virus genotype 1", section on 'Definitions'.)
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. Both quantitative and qualitative tests are used during treatment to assess response.

**Qualitative tests** — Qualitative tests are capable of detecting low levels of HCV RNA and are used for confirming the diagnosis of HCV infection and assessing sustained virologic responses (SVR) to antiviral therapy. They provide results as positive or negative and some have a lower limit of detection as low as <10 international units/mL HCV RNA. Examples of qualitative HCV RNA assays are Amplicor PCR assay (Roche Diagnostics) and Versant TMA assay (Siemens Healthcare Diagnostics). (See '[Methods of RNA detection](#)' above.)

**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. Assessment for treatment candidacy involves evaluation for factors that predict response to therapy, comorbidities that increase the urgency of treatment, and comorbidities that would be contraindications or complications for therapy. 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 to guide management decisions'.)

**History and physical exam** — Individuals with chronic hepatitis C should undergo a complete history and physical exam with a focus on assessing the extent of underlying liver disease and evaluating candidacy for treatment.

Thus, history should include questions regarding factors associated with accelerated disease progression, including alcohol use, metabolic complications associated with fatty liver, and menopausal status (in women), complications that would suggest underlying cirrhosis (eg, ascites, hematemesis, and mental status changes), and factors that may affect candidacy for antiviral therapy, including underlying cardiopulmonary disease, past or present psychiatric problems, autoimmune diseases, and other comorbid conditions.

Physical examination should include evaluation for stigmata of advanced liver disease such as spider angiomata, palmar erythema, splenomegaly, jaundice, or caput medusa. However, clinicians should be aware that absence of any of these findings does not rule out the possibility of underlying cirrhosis. Signs of extrahepatic manifestations of HCV infection, such as porphyria cutanea tarda should also be sought. (See "[Cirrhosis in adults: Etiologies, clinical manifestations, and diagnosis](#)", section on 'Physical examination' and "[Extrahepatic manifestations of hepatitis C virus infection](#)".)
Basic laboratory testing — Similarly, to assess the extent of underlying liver disease, evaluate for extrahepatic complications, and evaluate candidacy for treatment, initial laboratory testing should include:

- Serum aminotransferase activity
- Measures of synthetic function: Bilirubin, prothrombin time, and albumin
- Complete blood count
- Renal function, glucose, lipid panel, thyroid function tests
- Urinalysis
- 25-hydroxy vitamin D
- Pregnancy test for women of childbearing potential

Additionally, it is reasonable to evaluate for and exclude other causes of chronic liver disease, such as iron overload syndromes or autoimmune hepatitis, in patients with elevated aminotransferases. (See "Approach to the patient with abnormal liver biochemical and function tests", section on 'Elevated serum aminotransferases'.)

Because of the association between HCV and certain types of renal disease (eg, mixed cryoglobulinemia and membranoproliferative glomerulonephritis), HCV-infected patients should be screened for proteinuria, hematuria, hypertension, and renal function. Additional evaluation for cryoglobulinemia, complement levels, and rheumatoid factors, and potentially kidney biopsy may be warranted in the setting of significant proteinuria and/or impaired renal function. (See "Overview of renal disease associated with hepatitis C virus infection" and "Treatment of chronic hepatitis C infection in adults with renal impairment".)

Certain polymorphisms in or around the gene for IL28B, which is also called interferon lambda 3, have been associated with favorable response to treatment with pegylated interferon and ribavirin in patients with HCV infection (mainly genotype 1) (see "Predictors of a sustained virologic response following treatment with peginterferon and ribavirin for chronic hepatitis C virus infection", section on 'IL28B polymorphisms'). However, the clinical utility of testing IL28B genotypes is not clear as the predictive value is less with newer treatments. There are no trials that have evaluated whether such information can benefit prospective patient selection for therapeutic intervention or modification, particularly with the use of direct acting antiviral agents.
Similarly, some of these above laboratory testing (eg, thyroid function test) may be less relevant if the indicated treatment regimen does not contain interferon. (See "Treatment regimens for chronic hepatitis C virus genotype 1" and "Treatment regimens for chronic hepatitis C virus genotypes 2 and 3" and "Treatment regimens for chronic hepatitis C virus genotypes 4, 5, and 6.")

**HCV genotype testing** — Determination of HCV genotype, on which the regimen, dosing, and duration of therapy as well as likelihood of response depend, is essential to making decisions about treatment. This is discussed elsewhere. (See "Patient evaluation and selection for antiviral therapy for chronic hepatitis C virus infection", section on 'HCV genotype' and "Characteristics of the hepatitis C virus", section on 'Genotypes'.)

**Assessment of fibrosis stage** — Knowledge of the stage of fibrosis provides important prognostic information and guides certain decisions regarding treatment. Fibrosis stage can be assessed indirectly through history, physical examination, laboratory tests, and other noninvasive studies (such as the FibroSure and ultrasound-based transient elastography) or with liver biopsy. A detailed discussion on the assessment of fibrosis stage and the role of liver biopsy is found elsewhere. (See "Patient evaluation and selection for antiviral therapy for chronic hepatitis C virus infection", section on 'Assessment of fibrosis stage' and "Patient evaluation and selection for antiviral therapy for chronic hepatitis C virus infection", section on 'Role of liver biopsy'.)

**Testing for HIV, hepatitis B, and hepatitis A** — Patients diagnosed with HCV should also be tested for HIV and hepatitis B due to the common modes of transmission. Patients who are not immune to hepatitis B should be vaccinated to protect the liver from additional insults. In addition, patients should be tested for hepatitis A and vaccinated if not immune. (See "Screening and diagnostic testing for HIV infection" and "Diagnosis of hepatitis B virus infection" and "Overview of hepatitis A virus infection in adults" and "Immunizations for patients with chronic liver disease", section on 'Vaccines in chronic liver disease'.)

**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 5th to 6th 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 information: Hepatitis C (The Basics)"
- Beyond the Basics topic (see "Patient information: Hepatitis C (Beyond the Basics)"

**SUMMARY AND RECOMMENDATIONS**

- 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 diagnostic evaluation for chronic HCV typically begins with an antibody test. (See 'Diagnosis and testing approach' above.)
- If the antibody test is nonreactive, then chronic HCV infection is unlikely and testing can stop. Patients who are immunocompromised or 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.)
- A diagnostic approach to suspected acute hepatitis C is presented separately. (See "Clinical manifestations, diagnosis, and treatment of acute hepatitis C in adults", section on 'Diagnosis'.)
- A positive HCV RNA result is evidence of HCV infection. 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 'Reactive antibody and positive RNA test' above.)
- 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 when sensitive quantitative or qualitative tests with a low level of detection are used. A reactive antibody test in this setting is generally reflective of a false positive or past, cleared infection. (See 'Reactive antibody and negative RNA test' above.)
- 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 (NAT) 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 tests' above.)
Important aspects of initial care of the patient newly diagnosed with HCV involve evaluating the extent of liver damage and determining candidacy for treatment. Determination of HCV genotype, on which the regimen, dosing, and duration of therapy as well as likelihood of response depend, is essential to making decisions about treatment. Assessment for liver fibrosis through biopsy or noninvasive measures is helpful in guiding decisions regarding treatment (including treatment duration) and surveillance. (See 'Additional evaluation' above and "Patient evaluation and selection for antiviral therapy for chronic hepatitis C virus infection", section on 'Evaluation to guide management decisions'.)

Patients diagnosed with chronic HCV should also be tested for HIV, hepatitis B, and hepatitis A, and vaccination should be administered to those without immunity to the last two. Additionally, it is reasonable to evaluate for and exclude other causes of chronic liver disease, such as iron overload syndromes or autoimmune hepatitis, in patients with elevated aminotransferases. (See 'Testing for HIV, hepatitis B, and hepatitis A' above and "Approach to the patient with abnormal liver biochemical and function tests", section on 'Elevated serum aminotransferases'.)

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REFERENCES


## Indications to test for hepatitis C virus

<table>
<thead>
<tr>
<th>Indication</th>
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</thead>
<tbody>
<tr>
<td>History of illicit injection drug use or intranasal cocaine use, even if only used once</td>
</tr>
<tr>
<td>Receiving clotting factors made before 1987</td>
</tr>
<tr>
<td>Receiving blood/organs before July 1992</td>
</tr>
<tr>
<td>Receiving blood from a donor who tested positive for HCV</td>
</tr>
<tr>
<td>Children born to HCV-infected mothers</td>
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<tr>
<td>Needle stick injury or mucosal exposure to HCV-positive blood</td>
</tr>
<tr>
<td>Current sexual partner of an HCV-infected person</td>
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<tr>
<td>Evidence of liver disease (persistently elevated alanine aminotransferase [ALT] level)</td>
</tr>
<tr>
<td>Born in the United States between 1945 and 1965</td>
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<tr>
<td>Chronic hemodialysis</td>
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<tr>
<td>HIV infection</td>
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<tr>
<td>Incarceration</td>
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<tr>
<td>Extrahepatic manifestations of chronic hepatitis C virus infection (eg. porphyria cutanea tarda, mixed cryoglobulinemia)</td>
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</table>
### Signal to cut-off ratios suggestive of true positive anti-HCV antibody tests, by assay

<table>
<thead>
<tr>
<th>Screening test kit name</th>
<th>Manufacturer</th>
<th>Assay format</th>
<th>Signal-to-cut-off ratio predictive of a true positive ≥95 percent of the time</th>
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</thead>
<tbody>
<tr>
<td>Ortho HCV Version 3.0 ELISA Test System</td>
<td>Ortho</td>
<td>EIA (enzyme immunoassay)</td>
<td>≥3.8</td>
</tr>
<tr>
<td>Abbott HCV EIA 2.0</td>
<td>Abbott</td>
<td>EIA (enzyme immunoassay)</td>
<td>≥3.8</td>
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<tr>
<td>VITROS Anti-HCV</td>
<td>Ortho</td>
<td>CIA (chemiluminescent immunoassay)</td>
<td>≥8.0</td>
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<tr>
<td>AxSYM Anti-HCV</td>
<td>Abbott</td>
<td>MEIA (microparticle immunoassay)</td>
<td>≥10.0</td>
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<tr>
<td>Architect Anti-HCV</td>
<td>Abbott</td>
<td>CMIA (chemiluminescent microparticle immunoassay)</td>
<td>≥5.0</td>
</tr>
<tr>
<td>Advia Centaur HCV</td>
<td>Bayer</td>
<td>CIA (chemiluminescent immunoassay)</td>
<td>≥11.0</td>
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