Clinical manifestations, diagnosis, and treatment of acute hepatitis C virus infection in adults

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INTRODUCTION

By convention, acute hepatitis C virus (HCV) infection refers to the first six months of HCV infection following presumed HCV exposure [1]. While HCV infection is estimated to account for 15 percent of symptomatic cases of acute hepatitis in the United States, the majority of patients with acute HCV go undetected [2,3]. This is due in large part to the fact that patients with acute HCV are typically asymptomatic. In the United States, the Centers for Disease Control and Prevention estimated that there were 33,900 new HCV infections in 2015, of which only 2436 cases were reported [4]. This reflects a nearly three-fold increase in the incidence of HCV infection over a five-year period, which parallels the rising rates of injection drug use (figure 1).

This topic will review acute HCV in adults. Issues related to the transmission of HCV, screening for HCV, and managing patients with chronic HCV 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" and "Screening and diagnosis 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), are continuously updated, and can be accessed at www.hcvguidelines.org [5]. The discussion in this topic is generally consistent with those guidelines.

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

CLINICAL MANIFESTATIONS

Most patients who are acutely infected with HCV are asymptomatic. Symptomatic patients may experience jaundice, nausea, dark urine, and right upper quadrant pain. Patients with acute HCV infection typically have moderate to high serum aminotransferase elevations (see 'Laboratory findings' below). These may go undetected in asymptomatic patients.

Timing — Among patients who are symptomatic, symptoms typically develop 2 to 26 weeks after exposure to HCV, with a mean onset of 7 to 8 weeks [6]. The acute illness usually lasts for 2 to 12 weeks.

Symptoms — The majority of patients with acute HCV are asymptomatic. In a review that included five studies from the National Heart, Lung, and Blood Institute Study of Transfusion-Associated Non-A, Non-B, and Type C Hepatitis, more than two-thirds of patients with acute HCV were asymptomatic during the acute episode [7].

Among those patients presenting with symptomatic acute HCV infection, jaundice is commonly reported. In a study that included 51 patients with symptomatic acute HCV, patients reported jaundice (68 percent), dark urine and white stool (39 percent), nausea (34 percent), and abdominal pain (25 percent, predominantly right upper quadrant pain) [8]. Additional symptoms reported in other studies include fatigue, low-grade fever and chills, loss of appetite, pruritus, muscle aches, mood disturbances, joint pain, dyspepsia, and confusion [9].

Fulminant hepatic failure due to acute HCV infection is very rare but may be more common in patients with underlying chronic hepatitis B virus infection [10,11]. Conversely, spontaneous clearance of acute HCV infection is also more common in people with underlying current or past hepatitis B virus infection [12]. (See "Acute liver failure in adults: Etiology, clinical manifestations, and diagnosis".)

Laboratory findings — Aminotransferase levels are often greater than 10 to 20 times the upper limit of normal in patients with acute HCV, but can be highly variable [13-16]. In one of the

largest series that included 259 patients with acute HCV, the mean alanine aminotransferase was 1174 unit/L, with a range of 5 to 5185 unit/L (20 microkat/L, range 0.09 to 88 microkat/L) [15]. During the course of acute infection, aminotransferase levels can vary widely within short time intervals, in contrast to chronic infection, during which they are often elevated but relatively stable over time [9,17,18].

Among patients who develop symptoms, the aminotransferases start to increase shortly before the onset of clinical symptoms and usually before anti-HCV antibodies are detectable. However, since the levels often fluctuate (sometimes quite widely) and may even normalize, not all patients will have elevated aminotransferase levels at the time of presentation. Normalization of the serum aminotransferase concentrations after acute infection does not necessarily mean that the infection has cleared.

Patients with acute HCV infection may also have elevated total bilirubin levels [9,15,19,20]. In the study of 259 patients, 51 percent had a bilirubin level above 3 mg/dL (51 micromol/L) [15]. In a second study with 28 patients with acute HCV, the mean bilirubin concentration was 4.4 mg/dL (75 micromol/L) [19].

DIAGNOSIS

A detectable HCV RNA by polymerase chain reaction (PCR) in the setting of undetectable anti-HCV antibodies that subsequently become detectable within 12 weeks is generally considered definitive proof of acute HCV infection. Alternately, newly detectable HCV RNA and anti-HCV antibodies with documentation of negative tests within the prior six months is also diagnostic of acute HCV infection. In the absence of such documentation, the distinction between acute HCV infection and newly discovered chronic infection is not straightforward, since in both settings patients may have detectable HCV RNA, HCV antibodies, and elevated serum aminotransferases.

Diagnosing acute HCV infection is important as spontaneous clearance can still occur, treatment regimens may differ from those in chronic infection, and a careful history can identify risk factors for ongoing transmission. The approach to diagnosis of acute HCV infection differs slightly depending on the clinical presentation, whether the patient presents with acute hepatitis or with a distinct HCV exposure. This is discussed below.

Diagnostic approach — Acute HCV infection should be suspected in patients with clinical manifestations of acute hepatitis or with possible recent exposure to HCV (eg, needle-stick injury, recent injection drug use). Such patients should be tested for the presence of HCV RNA

and antibodies in the serum. The timing of testing is influenced by when HCV RNA and antibodies become detectable in the blood (figure 2 and figure 3).

Patients with acute hepatitis — For a patient presenting for the first time with acute hepatitis (eg, markedly elevated transaminases and/or jaundice), we immediately obtain HCV RNA by PCR and anti-HCV antibody testing by enzyme-linked immunosorbent assay (ELISA) (algorithm 1). Establishing the diagnosis of acute hepatitis C or the need for further testing for acute HCV depends on results of these tests:

- **HCV RNA negative** – Acute HCV infection is unlikely. Typically, HCV RNA is detectable by the time a patient has symptoms. If the HCV antibody is positive at this time point but the HCV RNA is negative, that is suggestive of a prior, cleared HCV infection, and this should be confirmed with repeat HCV RNA after 12 weeks. Follow-up confirmatory HCV RNA testing in this situation is important since HCV RNA levels can fluctuate widely during acute HCV infection and may even become transiently undetectable.

  In a person with acute hepatitis and repeatedly negative HCV RNA, an alternative etiology for acute hepatitis should be sought. (See "Approach to the patient with abnormal liver biochemical and function tests", section on 'Marked elevation without liver failure'.)

- **HCV RNA positive and HCV antibody negative** – Acute HCV infection is likely. We then either treat immediately (see 'Management' below) or recheck HCV RNA and anti-HCV antibody in 12 weeks (or a total of 12 weeks following a known or presumed exposure). Most patients will develop anti-HCV antibodies by 12 weeks after exposure, and it is preferable to make a diagnosis as soon as possible to help guide management. A positive anti-HCV result at this subsequent time point confirms seroconversion and acute HCV infection. Persistently detectable HCV RNA at 12 weeks indicates a high risk for subsequent chronic infection, whereas a negative HCV RNA suggests spontaneous viral clearance, which requires confirmation with repeat HCV RNA testing after another 12 weeks because HCV RNA can become transiently undetectable during acute infection. (See 'Spontaneous viral clearance' below.)

- **HCV RNA positive and HCV antibody positive** – This pattern confirms HCV infection, but in isolation, cannot distinguish between acute and chronic infection. If there is documentation of a serum sample within the prior six months with negative HCV RNA and anti-HCV antibody, then acute HCV infection is diagnosed. Similarly, if there is documentation of a recent negative HCV RNA following treatment or spontaneous clearance of a prior HCV infection, acute reinfection is likely. In the absence of such documentation, the distinction between acute HCV infection and newly discovered chronic

infection is not straightforward since, in both settings, patients may have detectable HCV RNA, anti-HCV antibodies, and elevated serum aminotransferases. In some cases, there is suggestive circumstantial evidence for new infection, such as a history of a recent high-risk exposure, new clinical features of acute hepatitis (including the degree of elevation of the transaminases), consistently normal aminotransferase levels on prior testing, and absence of risk factors for HCV infection in the past.

Repeat HCV RNA testing (eg, at least six weeks later) might help to distinguish acute from chronic infection in this setting. Fluctuating and/or low levels of HCV RNA are suggestive of acute HCV, whereas higher HCV levels that do not fluctuate are suggestive of chronic infection. As an example, in one report, low HCV RNA levels ($<10^5$ international units/mL) were seen in 17 of 21 patients with acute HCV (81 percent) compared with 81 of 623 patients with chronic HCV (13 percent) [17]. Viral load fluctuations during a 10-week period among those with acute HCV were >1 log in 18 patients (86 percent). In contrast, other studies have found that viral load fluctuations in chronic infection tend to be less than 1 log international units/mL over many years of infection [21,22]. (See "Clinical manifestations and natural history of chronic hepatitis C virus infection", section on 'Viral levels'.)

Similarly, aminotransferase levels fluctuate more widely in acute than chronic HCV infection. Markedly elevated alanine transaminase (ALT) levels in a patient with newly diagnosed HCV infection should raise suspicion for acute infection, particularly if history reveals recent risk exposures. Although there is no clearly defined threshold, we explore the possibility of acute HCV infection in patients with ALT levels above 300 units/L with no other explanation.

Finally, evidence of hepatic fibrosis can suggest chronic rather than acute infection, although this can be misleading if the patient has other potential causes of liver disease (such as heavy alcohol use). Fibrosis assessment is not needed to establish the diagnosis of HCV infection, but it can help differentiate acute from chronic HCV in cases where there is doubt. Noninvasive measures of fibrosis can be used instead of biopsy; however, the marked inflammation that can occur during acute HCV infection can falsely elevate fibrosis scores with transient elastography or serum panels that include aminotransferases (eg, APRI (calculator 1)or FIB-4 (calculator 2) calculations) [23]. (See "Noninvasive assessment of hepatic fibrosis: Overview of serologic tests and imaging examinations".)

For patients who have acute HCV infection, we repeat interval HCV RNA testing to evaluate for spontaneous clearance. (See 'Spontaneous viral clearance' below.)

In addition to diagnostic testing for acute HCV infection, evaluation of patients presenting with acute hepatitis includes testing for other causes (eg, hepatitis B virus infection, autoimmune hepatitis, hepatotoxicity). This is discussed in detail elsewhere. (See "Approach to the patient with abnormal liver biochemical and function tests", section on 'Elevated serum aminotransferases'.)

Patients with discrete HCV exposure — For a patient presenting following a known, discrete exposure to HCV (eg, needle-stick injury, recent injection drug use), we first obtain tests for HCV RNA, HCV Ab, and serum aminotransferases to establish the baseline HCV status (algorithm 2). Within one to two days following an exposure, a patient without prior infection should have negative HCV RNA, negative HCV Ab, and normal aminotransferases. Thus, this baseline HCV status can be used to document subsequent new seroconversion (if the exposure leads to infection) or to establish previously undiagnosed chronic HCV infection. Further testing depends on the results of the HCV RNA test:

- **Negative baseline HCV RNA** – Individuals who have negative HCV RNA at baseline are at risk for new HCV infection following an exposure. In such patients, we repeat testing to monitor for HCV infection:

  - Four weeks after exposure: HCV RNA and serum aminotransferases (anti-HCV antibody is not expected to be detectable at this time if it was negative at baseline)
  - Three to four months after exposure: HCV RNA, anti-HCV antibody (if not previously positive), and serum aminotransferases
  - Six months after exposure: HCV RNA, anti-HCV antibody (if not previously positive)

  Elevated aminotransferases at the above time points would be a trigger to check HCV RNA sooner if not already detectable.

  - **HCV RNA becomes detectable** – If the HCV RNA becomes detectable at one of the time points above, acute HCV infection is diagnosed. We then recheck anti-HCV antibody (if not already detected at one of these time points) 12 weeks later to confirm seroconversion and acute HCV. For such patients, we also repeat HCV RNA testing to evaluate for spontaneous clearance or initiate treatment. (See 'Spontaneous viral clearance' below and 'Management' below.)

  - **HCV RNA remains undetectable**

    - For patients who have a baseline positive anti-HCV antibody (suggestive of prior spontaneously cleared or treated HCV infection), if HCV RNA remains negative throughout the testing period outlined above, HCV reinfection has not occurred,

and testing can be stopped. If there is ongoing risk of exposure (eg, continued injection drug use or sexual exposure, particularly HIV-positive men who have sex with men), repeated screening for reinfection can be performed with HCV RNA testing [5].

- For patients who had a baseline negative anti-HCV antibody, if HCV RNA and anti-HCV antibody remain negative during the testing period, then HCV infection has not occurred, and testing can be stopped. In some cases, the anti-HCV antibody becomes reactive over time but the HCV RNA remains undetectable. This suggests acute HCV infection with spontaneous clearance and is confirmed when HCV RNA remains negative over 12 weeks and for at least six months after exposure. In rare instances, anti-HCV antibody may not become detectable after an acute infection, either because of a low inoculum with spontaneous clearance or an immunocompromising condition (eg, advanced HIV infection or hemodialysis), even if chronic infection ensues. With the newest generation HCV antibody assays, however, false-negative results are rare.

These recommendations for post-exposure testing are generally similar to those suggested by other expert guidelines, with slight differences in testing intervals [5,24,25]. As an example, in the United States, the Centers for Disease Control and Prevention recommend that, following an HCV exposure, health care personnel who have negative baseline HCV testing be tested with HCV RNA three to six weeks later [24]. If that HCV RNA test is negative, they should be tested again with anti-HCV antibody with reflex HCV RNA testing at four to six months; health care personnel who are immunocompromised or have underlying liver disease can be re-tested with HCV RNA at that time even if the anti-HCV antibody is negative. (See "Prevention of hepatitis B virus and hepatitis C virus infection among health care providers".)

Pre-exposure or post-exposure prophylaxis treatment is not recommended.

- **Detectable baseline HCV RNA** – Individuals with a detectable HCV RNA are HCV infected. If the anti-HCV antibody is also positive, this likely indicates preexisting chronic infection, although it can also represent an acute reinfection after prior spontaneous clearance or successful treatment. Aside from history, the level of ALT and other features mentioned above can help distinguish preexisting chronic infection from an acute reinfection. If the anti-HCV antibody is negative with a detectable baseline HCV RNA, this suggests acute HCV infection, particularly if the exposure was more than a few days prior. In such cases, we recheck the anti-HCV antibody at 12 weeks to confirm seroconversion and repeat HCV RNA testing to evaluate for spontaneous clearance. A small proportion of

immunocompromised individuals (eg, those with advanced HIV infection or on hemodialysis) may not develop antibodies; however, this is rare with the newest generation HCV antibody tests. (See 'Spontaneous viral clearance' below.)

HCV RNA timing and patterns — HCV RNA is first detectable in serum by PCR within days to eight weeks following exposure, depending, in part, upon the size of the inoculum [26,27]. In a series of 14 needle-stick injuries, a negative HCV PCR at two weeks post-exposure had a high negative predictive value (100 percent) [28]. However, the minimal interval following suspected exposure after which a persistently negative HCV PCR test excludes infection has not been definitely established. For patients with a discrete exposure, we typically test HCV RNA at baseline, at week 4, at weeks 12 to 16, and at 6 months. (See 'Patients with discrete HCV exposure' above.)

HCV RNA may remain detectable in the liver even in patients in whom it is undetectable in serum, although its clinical significance is uncertain [29].

HCV antibody timing and patterns — Enzyme-linked immunosorbent assay (ELISA) tests detecting anti-HCV antibodies become positive as early as eight weeks after exposure, with most patients seroconverting between two and six months after exposure (figure 2 and figure 3) [16,27]. Approximately one-half of patients with symptomatic acute infection have detectable anti-HCV antibodies by ELISA when first presenting [26]. Rare patients who are severely immunocompromised or on chronic dialysis do not mount a detectable anti-HCV antibody. (See "Screening and diagnosis of chronic hepatitis C virus infection", section on 'Nonreactive anti-HCV antibody'.)

A positive anti-HCV antibody does not distinguish acute or early infection from chronic infection or from a prior infection that has spontaneously cleared or was successfully treated. In addition, some patients with prior infection may have negative antibody testing because HCV antibody levels may eventually drop below detection limits in patients who have cleared the infection [30-32]. As a result, population-based studies that estimate spontaneous resolution rates of HCV infection using the prevalence of anti-HCV antibody positivity and HCV PCR negativity in untreated patients may underestimate spontaneous resolution rates.

DIFFERENTIAL DIAGNOSIS

In addition to acute HCV infection, the differential diagnosis of patients presenting with an elevation in aminotransferases, with or without symptoms of hepatitis, is broad and includes other infectious causes, toxin-mediated liver injury, metabolic disorders, and other systemic

illnesses. Differentiating among these entities requires a thorough history to identify risk factors for and symptoms of the various disorders as well as laboratory tests. Rarely, liver biopsy may be required if no cause for a patient's elevated aminotransferases can be determined noninvasively. The approach to the evaluation of a patient with abnormal liver tests is discussed in detail elsewhere. (See "Approach to the patient with abnormal liver biochemical and function tests" and "Acute liver failure in adults: Etiology, clinical manifestations, and diagnosis".)

MANAGEMENT

Counseling

Transmission risk and harm reduction — Upon confirmation or even suspicion of acute HCV infection, it is important to discuss recent risk exposures and evaluate for ongoing risk activities. All patients diagnosed with acute HCV infection have recently had some type of exposure.

In particular, injection drug use is the most common cause of acute HCV in North America and Europe. Harm-reduction strategies, including opiate agonist therapy, should be recommended for patients who use injection drugs to reduce transmission risk and to reduce the risk of overdose and other drug use-related harms. Harm-reduction strategies and directly observed HCV therapy may also help with engagement and adherence with antiviral therapy if treatment is initiated [33].

Patients should also be strongly encouraged to avoid or reduce specific activities associated with a risk of viral spread, particularly sharing needles or other drug-use equipment and high-risk sexual practices (table 1). The risk of sexual transmission is higher among men who have sex with men (MSM), particularly those who have HIV; acute HCV has also been reported among men using pre-exposure prophylaxis (PrEP) to prevent HIV infection [34]. Traumatic sex and sex under the influence of drugs have been more strongly associated with a risk of acute HCV transmission. (See "Epidemiology and transmission of hepatitis C virus infection", section on 'Routes of transmission' and "Screening and diagnosis of chronic hepatitis C virus infection".)

In addition, standard precautions, such as avoidance of sharing razors and toothbrushes, are advised.

Other precautions — Although liver failure in the setting of acute HCV infection is very rare, patients should be counseled to avoid additional hepatotoxic insults (such as alcohol or high-dose acetaminophen) in the setting of acute HCV infection. Medications that undergo hepatic metabolism generally do not have to be dose adjusted.

Risk of reinfection — Patients who achieve spontaneous viral clearance or sustained virologic response (SVR) after treatment should be aware that they remain at risk of reinfection if they are again exposed to HCV and require ongoing surveillance.

For those engaging in ongoing risk activities, repeat HCV screening every 6 to 12 months is recommended. For surveillance for reinfection, HCV RNA testing rather than HCV antibody testing must be used, as previously infected individuals will typically remain anti-HCV positive for life. (See "Screening and diagnosis of chronic hepatitis C virus infection", section on 'Those with ongoing risk'.)

Antiviral therapy — Our approach to the treatment of acute infection is largely consistent with the joint American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA) guidance, which recommends immediate treatment upon documentation of viremia in people with acute HCV infection [5]. The recommended regimens and durations are the same as those for chronic HCV infection (algorithm 3).

Whom to treat during acute infection — We generally suggest that patients undergo antiviral therapy during acute infection rather than waiting six months to determine whether chronic infection has been established because of the potential engagement and public health benefits of treating early. These benefits may be greatest with immediate treatment (eg, at the first detection of a positive HCV RNA), which is the approach endorsed by the joint AASLD/IDSA guidelines [5]. However, some patients may reasonably prefer to wait to see if they achieve spontaneous clearance and avoid unnecessary treatment. In this case, we typically recheck the HCV RNA at 12 weeks following the estimated date of infection (since most patients who spontaneously clear HCV will do so within this time frame) and initiate treatment if still detectable (see 'Spontaneous viral clearance' below). Patients who opt for this approach should be counseled on the need for follow-up and the risks of transmission. (See 'Counseling' above.)

Ultimately, however, some insurers require documentation of HCV infection for at least six months prior to covering direct-acting antiviral (DAA) regimens, and this greatly limits access for use in acute HCV infection. Patients who are not treated during acute infection should be evaluated for viral clearance and treated for chronic HCV, if established. (See 'Monitoring for viral clearance' below.)

Reasons to favor early (or immediate) treatment include:

- Concern that patients may be lost to follow-up while deferring treatment until chronic infection has been confirmed.

- Concern about ongoing transmission in patients who continue to engage in similar high-risk activities that resulted in the HCV infection. Modeling studies have suggested that treatment of people at high risk of ongoing transmission can reduce incidence and ultimately prevalence at the population level [35].

- The potential for severe acute HCV infection. (See 'Symptoms' above.)

Prior to the availability of DAA-based regimens for HCV treatment, there was impetus to treat patients within the first few months of infection, since the efficacy of interferon-based regimens during acute infection (with cure rates >90 percent) was greater than during chronic infection [36]. The high efficacy rates of DAA regimens for chronic HCV infection (cure rates >95 percent) reduce this efficacy benefit of treating early. Although shorter DAA regimens than those typically used in chronic infection might be effective for acute infection, optimal regimens have not yet been established, and the same regimens as those used for chronic infection are suggested, as below.

Regimen selection — When treating acute HCV infection, we suggest the same DAA regimens (with the same durations) that are recommended for treatment-naïve chronic infection (algorithm 3); specifically, we use sofosbuvir-velpatasvir for 12 weeks or glecaprevir-pibrentasvir for 8 weeks. These regimens are discussed in detail elsewhere. (See "Management of chronic hepatitis C virus infection: Antiviral retreatment following relapse in adults", section on 'Regimen selection for relapse after DAA therapy' and "Management of chronic hepatitis C virus infection: Initial antiviral therapy in adults", section on 'Selecting among preferred regimens'.)

Data on the outcomes with DAA therapy during acute infection are limited but emerging [37-42]. Abbreviated regimens have been evaluated for acute HCV, but they may not be as effective as standard duration regimens used for chronic infection.

In the only randomized controlled trial of treatment during acute or recent HCV infection (the international multicenter REACT study), patients who presented within 12 months of infection were assigned to sofosbuvir-velpatasvir for six weeks or the standard 12 weeks [43]. The study was stopped early because of lower treatment response in the six-week treatment group (SVR rates of 81 percent [76 of 93 patients] versus 91 percent [86 of 95 patients] with 12 weeks). Excluding those with nonvirologic failure (death, reinfection, loss-to-follow-up), SVR rates were 90 versus 98 percent in the 6- versus 12-week arms. The main difference in SVR rate was due to a higher relapse rate with six weeks of treatment (10 versus 2 percent). No clinical or virologic predictors of relapse were identified.

Thus, we use sofosbuvir-velpatasvir for 12 weeks when chosen for treatment during acute HCV infection. We extrapolate these data to favor using the standard duration with other regimens as well; however, high SVR rates have been described with shorter durations for certain regimens:

- Glecaprevir-pibrentasvir – Six weeks may be a reasonable alternative to the standard eight-week duration for patients with acute infection. In an open-label, single-arm study of 30 patients with recent HCV infection, glecaprevir-pibrentasvir for six weeks resulted in an SVR rate of 90 percent; there was only one virologic failure [38].

- Ledipasvir-sofosbuvir – Single-arm, non-controlled studies have reported high SVR rates with eight or even six weeks of therapy [39-42]. Although results differ slightly between studies, an HCV RNA level >7 log international units/mL is associated with viral relapse. Thus, we suggest **not** shortening duration to less than 12 weeks in patients with HCV RNA levels >7 log international units/mL. In a trial of 20 patients with acute genotype 1 HCV infection (identified through seroconversion or suspected exposure with newly elevated aminotransferases within the past four months), all achieved SVR with six weeks of ledipasvir-sofosbuvir [39]. In another trial of 26 MSM with HIV and mostly asymptomatic acute genotype 1a or genotype 4 HCV infection, six weeks of ledipasvir-sofosbuvir resulted in SVR in 77 percent [40]. Of the six participants who did not achieve SVR, virologic relapse was documented in three, all of whom had viral levels >6.9 log international units/mL. Two others were lost to follow-up after achieving SVR4, and one patient was reinfected before the SVR12 time point, highlighting the need for ongoing surveillance in this often high-risk population.

Overall, treatment outcomes for acute HCV in patients with HIV appear similar to those in patients without HIV, as in chronic HCV infection [40-42].

Similar to the excellent safety and tolerability in chronic infection, DAAs are well tolerated when used in acute infection.

Interferon-based regimens are no longer used in locations where DAA regimens are available.

Assessing treatment response — Virologic response to treatment is assessed by checking the viral load at 12 weeks following the cessation of therapy. It is not clear that any other specific measurement of HCV RNA during or at the end of treatment is necessary or useful.

For those who do not achieve SVR, further management is the same as for chronic HCV infection. (See "Overview of the management of chronic hepatitis C virus infection".)

SPONTANEOUS VIRAL CLEARANCE

Without antiviral therapy, patients infected with HCV either spontaneously clear the virus or go on to develop chronic infection. (See "Clinical manifestations and natural history of chronic hepatitis C virus infection".)

Monitoring for viral clearance — Once acute HCV infection has been diagnosed, the patient should be monitored to determine the outcome of infection (spontaneous viral clearance versus chronic infection) if the patient does not undergo immediate antiviral treatment. This is done by retesting HCV RNA over a period of time; the frequency depends on treatment decisions. (See 'Whom to treat during acute infection' above.)

- If the decision to treat during acute infection has been made but the patient wants to wait to check for spontaneous clearance to try to avoid potentially unnecessary treatment, we check HCV RNA at 12 weeks following exposure (or following diagnosis if the infection date is unknown). Spontaneous clearance is likely in those who have a negative HCV RNA at this time point. Those who have a positive HCV RNA at this time point can proceed to therapy. (See 'Antiviral therapy' above.)

- If the patient is not going to be treated during acute infection, we monitor HCV RNA over six months to allow identification of spontaneous clearance. Spontaneous clearance is likely in those who have a negative HCV RNA within six months. Those who have a positive HCV RNA after six months are considered to have chronic HCV infection, although it is reasonable to recheck HCV RNA after another six months, particularly if the aminotransferase levels normalize, as late clearance of acute infection has been described [44]. Stabilizing HCV RNA and alanine transaminase (ALT) levels signify the onset of chronic infection, at which point spontaneous clearance is extremely unlikely to occur.

Patients who appear to have cleared HCV RNA should have subsequent HCV RNA determinations to ensure that clearance was sustained (ie, at least two negative HCV RNA tests at least 12 weeks apart and at least 6 months beyond the estimated date of exposure).

For patients who have established chronic HCV infection, additional evaluation is discussed elsewhere. (See "Screening and diagnosis of chronic hepatitis C virus infection", section on 'Additional evaluation'.)

Likelihood of spontaneous viral clearance — Estimates of the frequency of spontaneous viral clearance vary from 14 to 50 percent [8,27,30,45-56]. Several more recent studies of acute HCV infection report spontaneous viral clearance around 50 percent [57-62].

A number of biologic factors are associated with spontaneous clearance. Patients with symptomatic acute HCV infection are more likely to have spontaneous clearance than asymptomatic patients [8,53,63,64]. In a study of patients with acute HCV, spontaneous clearance occurred in 24 of 46 patients (52 percent) who were symptomatic and in 0 of 9 who were asymptomatic [8]. Symptoms are thought to reflect a more robust immune response targeting the virus, which leads to more rapid HCV RNA decline and increases the likelihood of clearance [18,46,56,65].

Other factors consistently associated with a higher chance of spontaneous clearance include younger age at acquisition, female sex [55,66], genotype 1 (versus non-1 [55]), and polymorphisms in the interferon-lambda 4 gene [55,56,66-68]. Chronic or resolved (ie, HBsAg-negative and anti-HBc-positive) hepatitis B infection is also associated with spontaneous clearance, whereas HIV coinfection is associated with persistence [12,69]. Those who have previously had spontaneous clearance are more likely to have clearance again upon reinfection, but clearance of chronic infection following successful treatment does not appear to influence the risk of spontaneous clearance following reinfection [66,70].

The wide variability in estimated clearance rates across studies may be due, in part, to the study methodology used. Because not all exposed individuals develop antibodies and antibody titers wane over time and may eventually disappear, spontaneous clearance rates may be underestimated by population-based studies that use the prevalence of anti-HCV antibody positivity and HCV PCR negativity in untreated patients to identify clearance. Consistent with this explanation, prospective studies consistently report higher clearance rates than retrospective population-based studies. In addition, for those with ongoing risk factors, such as continued injection drug use, some episodes of spontaneous clearance may be missed if reinfection occurs in between testing intervals. This may, in part, explain the relatively low rates of clearance (20 percent or less) among people who use injection drugs [60,71,72].

Timing of viral clearance — Most patients who are destined to spontaneously clear HCV viremia do so within 12 weeks [8,18,73].

As an example, in a study of 27 patients with acute HCV infection who were not receiving treatment, 8 patients (30 percent) spontaneously cleared the virus, 88 percent of whom did so before week 12 (with the final patient doing so at week 14) [73].

However, spontaneous clearance after longer follow-up, up to two years after initial infection, has also been described, although this may be in part related to differing methodology [44]. The International Collaboration of Incident HIV and Hepatitis C in Injecting Cohorts (InC3) combined cohorts of people who actively injected drugs, were anti-HCV negative at entry, and underwent

routine serial screening for HCV infection [55]. Of 632 individuals in whom acute HCV infection was diagnosed through seroconversion, 25 percent spontaneously cleared the virus within one year, at a median of 16 weeks after the estimated date of infection. Among those who cleared, 34, 67, and 83 percent had cleared the virus by 3, 6, and 12 months, respectively. Although this is one of the largest studies to evaluate spontaneous HCV clearance, the longer times to clearance compared with smaller studies may be due, in part, to the methodology used to estimate the date of infection (defined in this study as the midpoint between the last negative and the first positive HCV antibody test). It is likely that the date of infection estimated by this approach was earlier than the true date of infection for many individuals, and this would result in longer estimated times to clearance.

Patients who achieve spontaneous viral clearance should be aware that they remain at risk of reinfection if they are again exposed to HCV. Although the antibody to HCV is not protective against reinfection, reinfection after spontaneous clearance is associated with a shorter duration, lower peak of viremia, and a higher chance of spontaneous clearance, suggesting a degree of protective immunity [66].

Once chronic infection ensues, typically an average of six months after exposure, spontaneous clearance is very infrequent. Nevertheless, long-term follow-up studies have documented that spontaneous clearance of chronic infection does occasionally occur. In a large Scottish study, spontaneous clearance was reported at a rate of 0.36 per 100 person-years [44]. Factors associated with clearance were female sex, younger age at infection, lower baseline HCV RNA level, and coinfection with hepatitis B virus.

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

SUMMARY AND RECOMMENDATIONS

- **Definition** – Acute hepatitis C virus (HCV) infection refers to the first six months of HCV infection following presumed HCV exposure. (See 'Introduction' above.)
- **Clinical suspicion and evaluation** – Most patients with acute HCV infection are asymptomatic; those who develop symptoms do so approximately seven to eight weeks after infection. Acute HCV infection should be suspected in patients with clinical manifestations of an acute hepatitis syndrome (eg, markedly elevated transaminases and/or jaundice) or with possible recent exposure to HCV (eg, from a needle-stick or injection drug use). (See 'Clinical manifestations' above.)
  - For a patient presenting for the first time with acute hepatitis possibly due to HCV exposure, we immediately obtain HCV RNA by PCR and anti-HCV antibody testing by enzyme-linked immunosorbent assay (ELISA). Establishing the diagnosis of acute hepatitis C or the need for further testing for acute HCV depends on results of these tests (algorithm 1). (See 'Patients with acute hepatitis' above.)
  - For a patient presenting following a known, potential exposure to HCV, we first obtain tests for HCV RNA, HCV Ab, and serum aminotransferases to establish the baseline HCV status. Among those who are uninfected at baseline, we recheck these tests intermittently (at least after three and six months) to evaluate for new HCV infection (algorithm 2). (See 'Patients with discrete HCV exposure' above.)
- **Diagnosis** – A detectable HCV RNA by polymerase chain reaction (PCR) in the setting of undetectable anti-HCV antibodies that subsequently become detectable within 12 weeks is generally considered definitive proof of acute HCV infection.

Alternately, newly detectable HCV RNA and anti-HCV antibodies with documentation of negative tests within the prior six months is also suggestive of acute HCV infection. In the absence of such documentation, the distinction between acute HCV infection and newly discovered chronic infection is not straightforward. (See 'Diagnosis' above.)

- **Rate and timing of spontaneous vial clearance** – Approximately 14 to 50 percent of patients acutely infected with HCV spontaneously clear the virus; the remainder go on to develop chronic infection. Most patients who are destined to spontaneously clear HCV viremia do so within 12 weeks, although clearance after longer follow-up (as long as two years) has been described. (See 'Spontaneous viral clearance' above.)

- **When to treat acute HCV infection** – For most patients, we suggest antiviral treatment during acute infection rather than waiting six months until chronic infection is established (**Grade 2C**). Treatment can be initiated immediately (eg, as soon as viremia is detected) or, for those who prefer to reduce the risk of unnecessary treatment, once detectable HCV RNA is documented 12 weeks following the estimated date of infection. Patients who are not treated during acute infection should be evaluated for treatment for chronic HCV infection if clearance has not occurred by six months. (See 'Whom to treat during acute infection' above and 'Monitoring for viral clearance' above.)

- **Antiviral selection** – For antiviral treatment during acute infection, we suggest the same regimens and duration as recommended for chronic infection (algorithm 3) (**Grade 2B**). These regimens are either sofosbuvir-velpatasvir for 12 weeks or glecaprevir-pibrentasvir for eight weeks; they can be used for any genotype. Virologic response to treatment is assessed by checking the viral load at 12 weeks following the cessation of therapy. (See 'Regimen selection' above and 'Assessing treatment response' above.)

- **Counseling and harm reduction** – Patients who achieve spontaneous viral clearance or sustained virologic response after treatment should be aware that they remain at risk of reinfection if they are again exposed to HCV. Assessment and management of ongoing injection drug use are important to ensure optimal HCV outcomes and to avoid drug use-related complications. (See 'Counseling' above and 'Transmission risk and harm reduction' above.)

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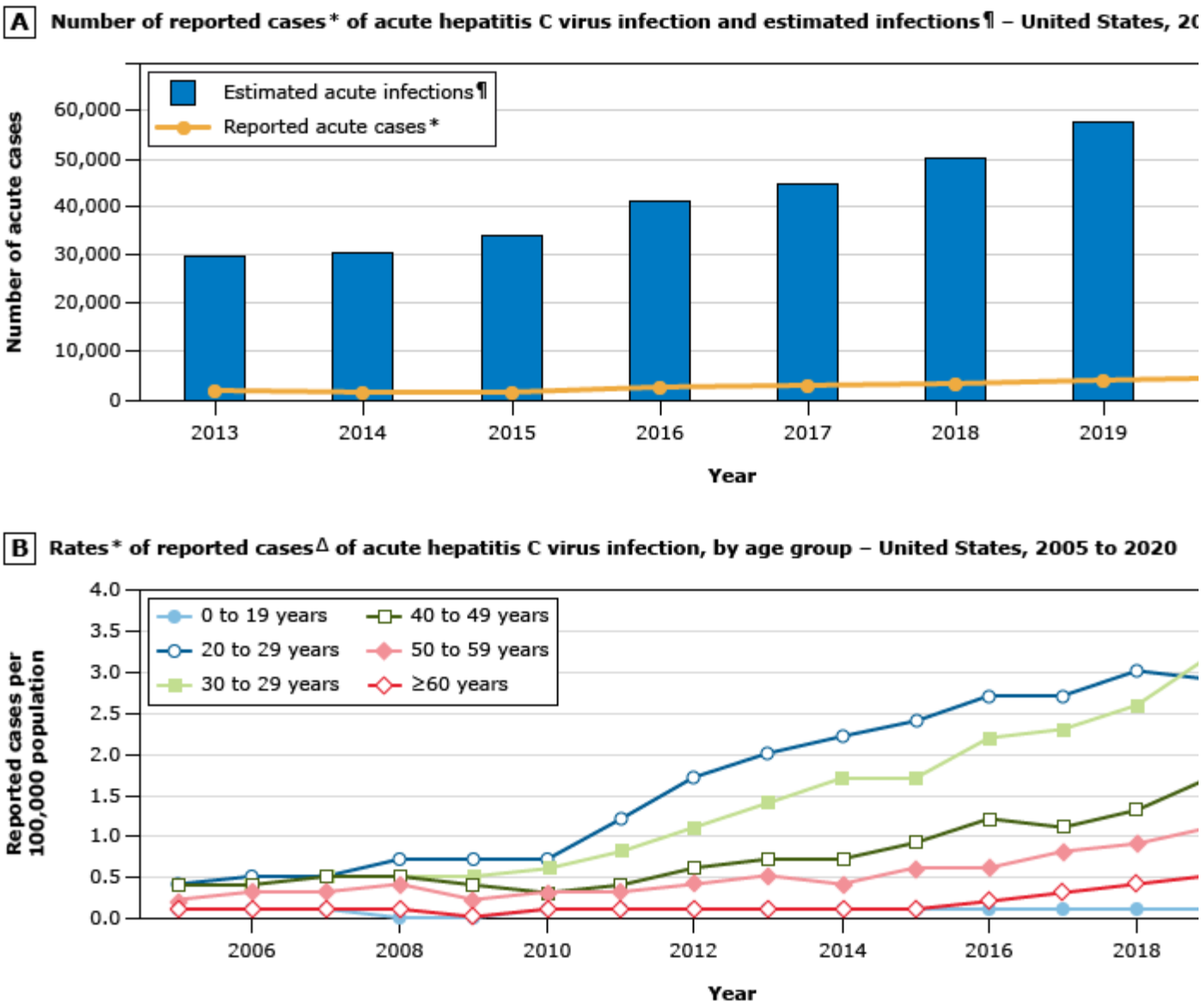
Topic 3650 Version 40.0

GRAPHICS

Incidence of hepatitis C virus cases in the United States, 2013 to 2020



* Reported confirmed cases.

¶ The number of estimated viral hepatitis infections was determined by multiplying the number of reported met the classification criteria for a confirmed case by a factor that adjusted for underascertainment and underreporting.

△ Rates per 100,000 population.

Reproduced from: Viral Hepatitis Surveillance – United States: 2020 Surveillance, Hepatitis C. Centers for Disease Control and Preventi at: https://www.cdc.gov/hepatitis/statistics/2020surveillance/hepatitis-c.htm (Accessed October 13, 2022).

Graphic 116122 Version 2.0

Serologic pattern of acute HCV infection with progression of chronic infection

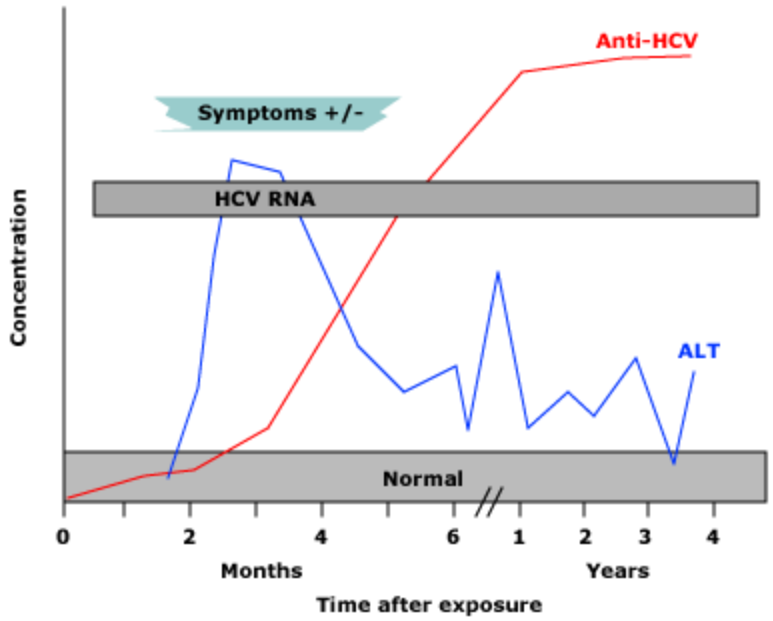


Figure provided by the Centers for Disease Control and Prevention.

Graphic 68723 Version 1.0

Time course of acute HCV infection with recovery

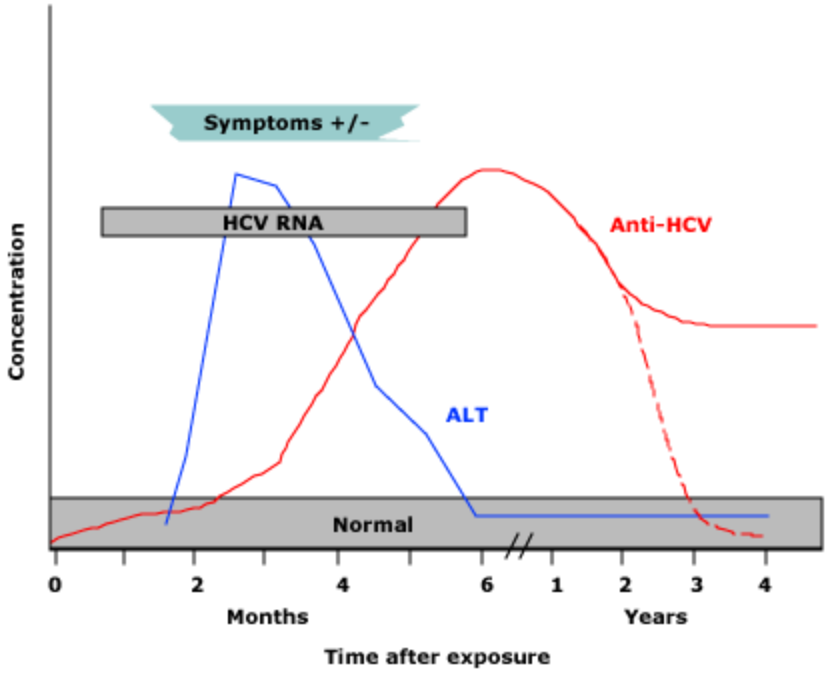
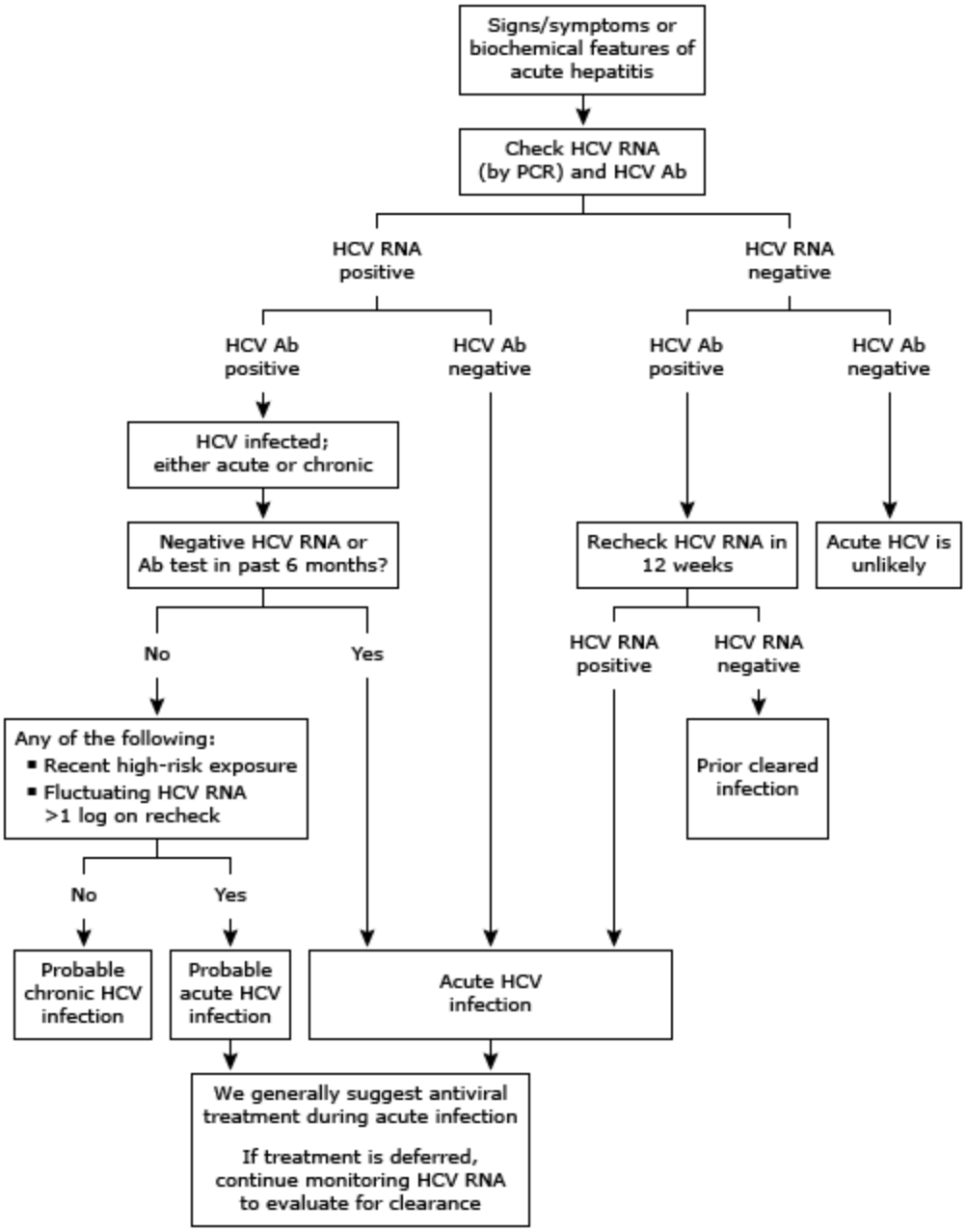


Figure adapted from: the Centers for Disease Control and Prevention.

Graphic 60223 Version 1.0

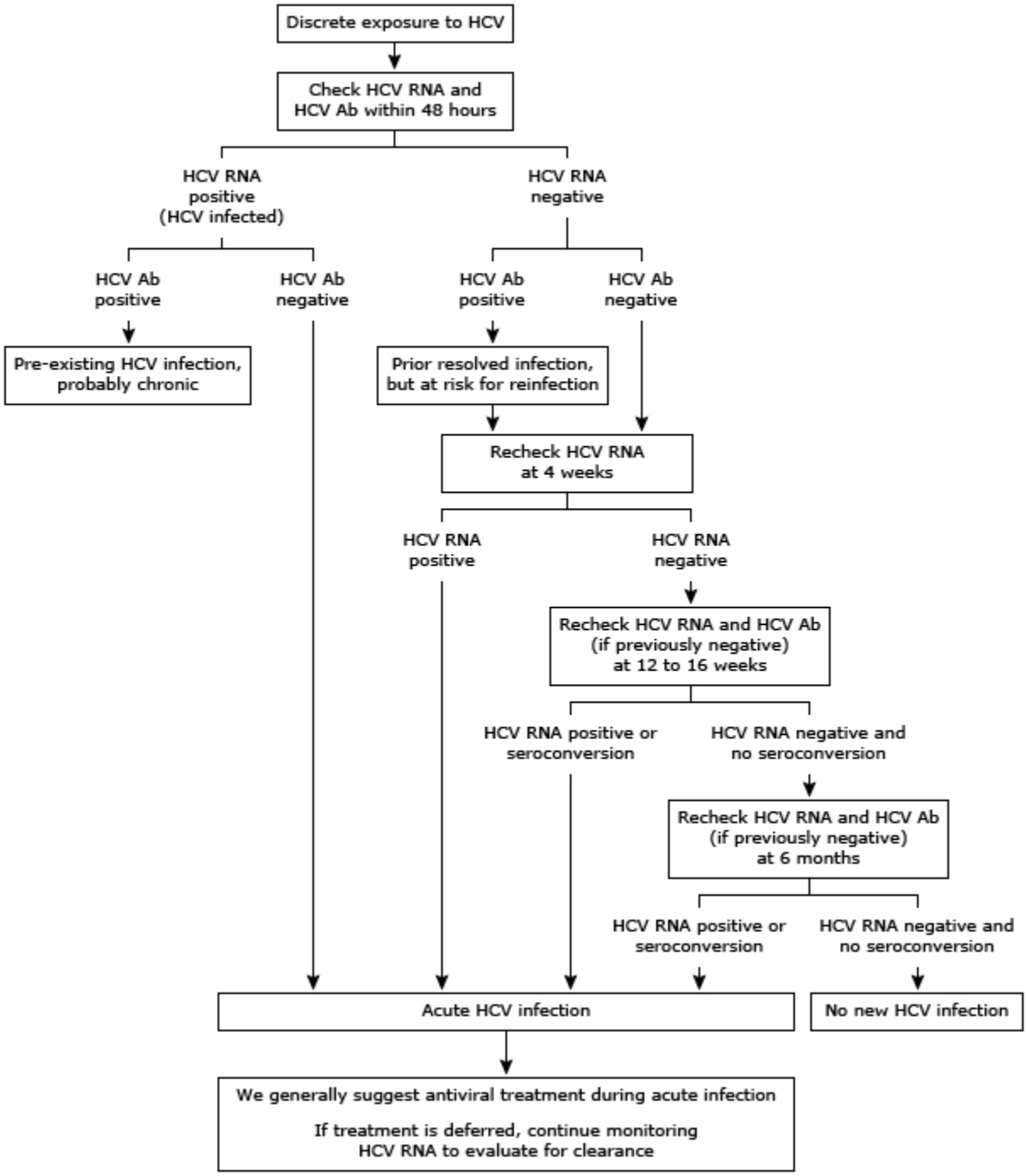
Evaluation for acute HCV infection in a patient with acute hepatitis



HCV: hepatitis C virus; PCR: polymerase chain reaction; Ab: antibody.

Graphic 101863 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.

HCV: hepatitis C virus; Ab: antibody.

Graphic 101864 Version 3.0

Counseling to avoid transmission of hepatitis C virus

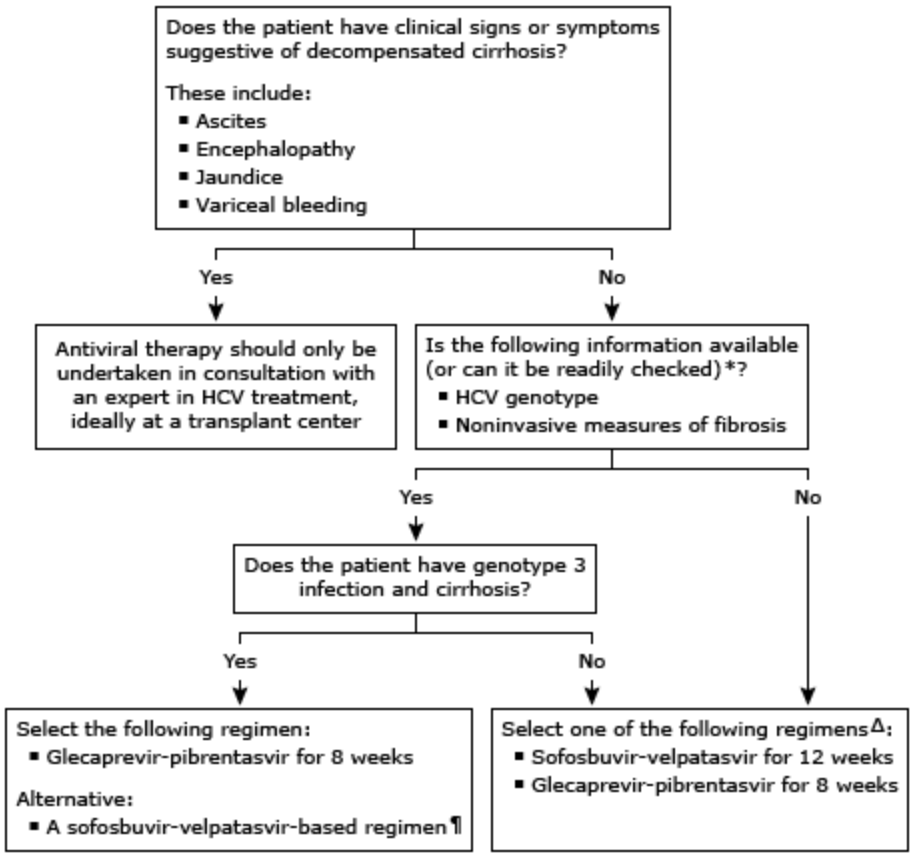
Individuals with HCV infection should be counseled to: ▪ Avoid sharing toothbrushes and dental or shaving equipment ▪ Cover any bleeding wound to prevent others from coming into contact with their blood ▪ Not donate blood ▪ Discuss their HCV status prior to donation of body organs, other tissues, or semen
In general, individuals with HCV infection should be counseled that the risk of sexual transmission is low and that HCV infection itself is not a reason for barrier protection. However, individuals with HCV infection who have HIV co-infection, multiple sexual partners, or sexually transmitted infections should be encouraged to use barrier precautions to prevent sexual transmission.
Individuals with HCV infection who use illicit drugs should be counseled to: ▪ Get treated for substance use disorder Those who inject drugs should be counseled to: ▪ Avoid reusing or sharing syringes, needles, water, cotton, and other drug preparation equipment ▪ Use new sterile syringes and filters and disinfected cookers ▪ Clean the injection site with a new alcohol swab ▪ Dispose safely of syringes and needles after one use in a safe, puncture-proof container
Household surfaces or items visibly contaminated with blood from an individual with HCV infection should be cleaned using diluted household bleach (1 part bleach in 9 parts water). Gloves should be worn when cleaning blood spills.

HCV: hepatitis C virus.

Adapted from: AASLD-IDSA. HCV testing and linkage to care. Recommendations for testing, managing, and treating hepatitis C. Available at: http://www.hcvguidelines.org/full-report/hcv-testing-and-linkage-care (Accessed July 8, 2016).

Graphic 58787 Version 5.0

Regimen selection for initial therapy of chronic HCV infection



This algorithm reflects our approach to initial therapy, for which we prioritize simplifying care to reduce barriers to access. The measured outcome of therapy is SVR, which is defined as an undetectable HCV viral level 12 weeks after the completion of therapy and reflects effective cure of infection. For additional details, including the evidence supporting this approach, refer to other UpToDate content on treatment of chronic HCV infection.

SVR: sustained virologic response.

* For initial therapy, knowledge of the HCV genotype and stage of fibrosis is not essential to selecting an antiviral regimen, as the preferred options are highly effective for all patients, regardless of genotype and cirrhosis. However, if these results are already available or if obtaining them does not pose a potential barrier to treatment, the information can be used to tailor regimen selection for a small subset of patients, which may increase their likelihood of SVR by a few percentage points.

¶ In patients with genotype 3 and cirrhosis, testing for the Y93H NS5A resistance-associated substitution is used to guide the optimal

sofosbuvir-velpatasvir-based regimen. Because this testing is not always readily available, we generally favor glecaprevir-pibrentasvir for such patients. Refer to other UpToDate content for more details.

Δ The selection between sofosbuvir-velpatasvir and glecaprevir-pribrentasvir is often dictated by access (eg, payers may only reimburse one of the options). If both are accessible, the choice between them depends on the potential for drug interaction and patient preference regarding practical administration issues.

Graphic 93587 Version 15.0

Contributor Disclosures

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