Management of Acute HCV Infection

Acute hepatitis C infection is most often asymptomatic and frequently develops into chronic infection. Case reports of acute hepatitis C in the US increased yearly from 2010 through 2021. Although there was a 6% decrease in acute hepatitis C infections in 2022, the number of cases in 2022 was still 2 times as high as the number of cases in 2015 (CDC, 2024). Acute HCV infection has most often been associated with parenteral exposures to blood or body fluids (CDC, 2019). Although HCV infection is primarily associated with injection drug use (IDU), certain behaviors—for example, unprotected (without a condom) receptive anal intercourse primarily among men who have sex with men (MSM)—are risk factors for transmission (Lockart, 2019); (Price, 2019). The syndemic of opioid use disorder and HCV and HIV transmission contributes to the burden of disease in certain populations (Butt, 2020).

Diagnosis of Acute HCV Infection

Recommended Testing[a] for Diagnosing Acute Hepatitis C Virus Infection	
RECOMMENDED	RATING
HCV antibody and HCV RNA testing are recommended when acute hepatitis C infection is suspected due to exposure, clinical presentation, or elevated aminotransferase levels (see Testing Algorithm figure).	I, C
[a] Recommendations for hepatitis C virus testing are also found in the Testing and Linkage to Care section.	

Diagnosis of acute HCV infection enables estimation of annual incidence rates and transmission patterns, thereby facilitating implementation and assessment of prevention programs. At the individual level, a diagnosis of acute infection expedites linkage to care, counseling regarding high-risk behavior, and timely interventions to reduce virus transmission and liver disease progression (Bruneau, 2014). Some persons involved in high-risk behaviors practice serosorting, defined as using HCV antibody serostatus to determine whether to engage in high-risk behaviors with certain individuals (Smith, 2013). Thus, undiagnosed acutely infected persons may be at greater risk of transmitting HCV to their presumably seronegative contacts than would be expected by chance.

The best laboratory evidence to support a diagnosis of acute HCV infection is a positive HCV RNA test in the setting of a negative HCV antibody test (identification during the seronegative window period) (Cox, 2005), or a positive HCV antibody test after a prior negative HCV antibody test (seroconversion). There are rare instances in which these approaches may be misleading, such as in immunosuppressed individuals with impaired antibody production (Chamot, 1990).

Discrete Exposure

The aforementioned types of clear, laboratory-based documentation of acute HCV infection are most easily achieved when there has been a discrete, known or suspected exposure (eg, after new onset or a change in

drug injection practice, a percutaneous needle stick exposure to an individual with HCV infection, a potentially nonsterile tattoo, or sexual assault). In those instances, baseline HCV antibody and HCV RNA testing should be done within 48 hours of the exposure to document whether there was antecedent HCV infection (see Testing Algorithm figure).

If baseline testing is negative, repeat testing is recommended. Frequency of testing can be tailored based on management objectives (eg, monthly testing to identify and treat acute infection). If baseline HCV antibody testing is positive but HCV RNA testing is negative, repeat HCV RNA and alanine aminotransferase (ALT) testing is recommended to identify an acute reinfection. When baseline HCV antibody and HCV RNA testing are both positive, the person most likely already has chronic HCV infection from prior exposure(s).

No Discrete Exposure

Individuals suspected of having acute HCV infection often do not have a discrete exposure or have no prior baseline testing making a diagnosis of acute infection more difficult (see Blood Test Interpretation Table). Acute infection should be suspected if there is a new rise in the ALT level without an alternative cause (Kim, 2013); (Blackard, 2008). Acute infection should also be suspected when there are low (especially <104 IU/mL) or fluctuating (>1 $\log_{10}$ IU/mL) HCV RNA values or spontaneous clearance. These patterns do not commonly occur outside of the first 6 months after HCV infection (McGovern, 2009). In those with a high index of suspicion for HCV exposure (eg, recently relapsed IDU or other high-risk exposure), an HCV RNA should be repeated if negative.

Persons suspected of having acute HCV infection should also have a laboratory evaluation to exclude other or coexisting causes of acute hepatitis (eg, hepatitis A virus, hepatitis B virus, hepatitis delta virus if chronically infected with hepatitis B virus, and autoimmune hepatitis) (Kushner, 2015). In persons with sexual acquisition of acute HCV infection, evaluation for concurrent genital ulcerative disease and proctitis is recommended (Todesco, 2019); (Goldenberg, 2017). HIV testing should also be performed.

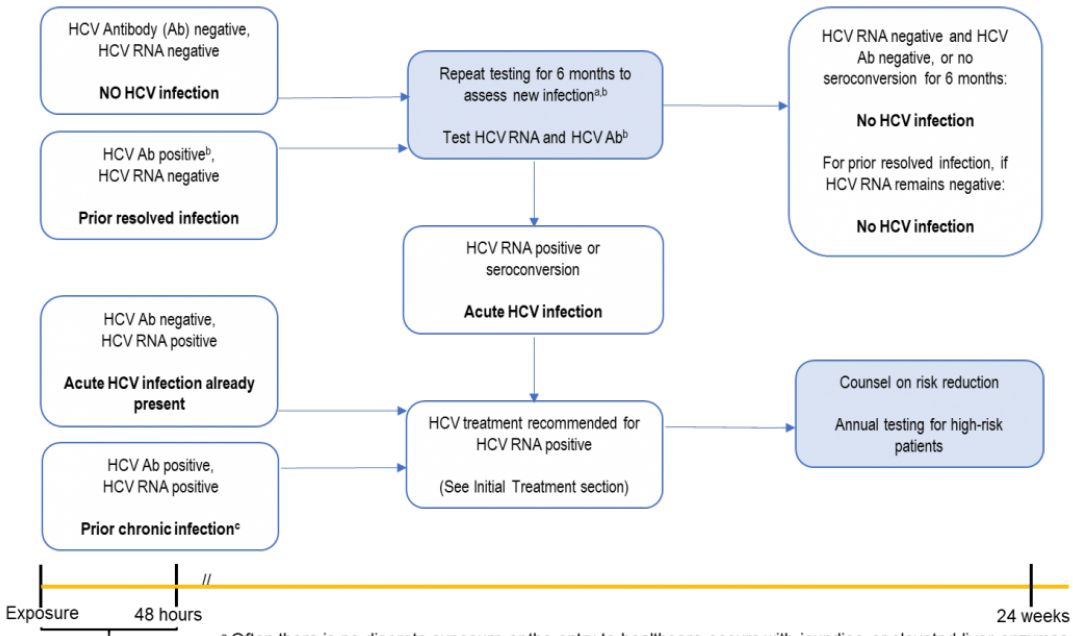
Interpretation of Blood Tests for Diagnosis of Acute HCV Infection

Test	Interpretation for Diagnosis of Acute HCV Infection
HCV Antibody	• Test may be negative during the first 6 weeks after exposure. • Seroconversion may be delayed or absent in immunosuppressed individual, eg, persons with HIV and CD4 <200 cells/mm^3 • The presence of HCV antibody alone does not distinguish between acute versus chronic infection.
HCV RNA	• Viral fluctuations >1 $\log_{10}$ IU/mL may indicate acute HCV infection. • HCV RNA may be transiently negative during acute HCV infection. • The presence of HCV RNA alone does not distinguish between acute

Test	Interpretation for Diagnosis of Acute HCV Infection
	versus chronic infection.
ALT	• Fluctuating ALT peaks suggest acute infection. • ALT may be normal during acute HCV infection. • ALT may be elevated due to other liver insults, such as alcohol consumption.

ALT, alanine aminotransferase; CD4, CD4-positive T lymphocytes; HCV, hepatitis C virus; HIV, human immunodeficiency virus; RNA, ribonucleic acid.

Figure 1. Testing Algorithm for Discrete Recognized Hepatitis C Virus (HCV) Exposure[a]



[a] Often there is no discrete exposure or the entry to healthcare occurs with jaundice or elevated liver enzymes. In those instances, baseline testing cannot be performed and the diagnosis of acute infection is more challenging (see text).

[b] Repeat HCV Ab is not needed if the test is positive at baseline. Frequency of testing can be tailored based on risk of exposure.

[c] If there were additional exposures in the preceding 6 months, a patient with a new diagnosis who is HCV RNA and HCV Ab positive may still be in the acute infection phase. Symptoms, high ALT level, or viral fluctuations may distinguish acute from chronic HCV.

[d] Baseline testing should be done within 48 hours of exposure to determine existing infection status, including HCV RNA, HCV Ab, and ALT.

Pharmacologic Prophylaxis

Pharmacologic Prophylaxis Not Recommended	
NOT RECOMMENDED	RATING
Pre-exposure or post-exposure prophylaxis with antiviral therapy is not recommended.	III, C

There are no data on the efficacy or cost-effectiveness of antiviral therapy for pre-exposure or post-exposure prophylaxis of HCV infection.

Medical Management and Monitoring of Acute HCV Infection

Recommendations for Medical Management and Monitoring of Acute HCV Infection	
RECOMMENDED	RATING
After the initial diagnosis of acute HCV infection with viremia (defined as quantifiable RNA), HCV treatment should be initiated without awaiting spontaneous resolution.	I, B
Counseling is recommended for persons with acute HCV infection to avoid hepatotoxic insults, including hepatotoxic drugs (eg, acetaminophen) and alcohol consumption, and to reduce the risk of HCV transmission to others.	I, C
Referral to an addiction medicine specialist is recommended for persons with acute HCV infection related to substance use.	I, B

People with acute HCV infection should be treated upon initial diagnosis without awaiting spontaneous resolution, using a test-and-treat strategy and according to the simplified approach, if eligible. Real-world data have demonstrated a reduction in HCV viremia prevalence and incidence with unrestricted access to HCV therapy (Boerekamps, 2018). In addition, mathematical modeling suggests that direct-acting antiviral (DAA) treatment scale-up, especially among those at highest risk of transmission, can reduce HCV incidence and prevalence (Martin, 2013); (Martin, 2016). Moreover, delay introduced by waiting for spontaneous clearance may be associated with loss to follow-up.

Individuals with acute HCV infection should be counseled to reduce behaviors that could result in virus transmission, such as sharing injection equipment and engaging in high-risk sexual practices. Because the risk of transmission of other bloodborne, sexually transmitted infections (eg, HIV and HBV) is higher in the acute infection phase, some experts counsel persons with acute HCV infection to consider using barrier precautions, even in a stable monogamous relationship (see Testing and Linkage to Care). For individuals with acute HCV

infection who have a history of recent IDU, referral to harm reduction services and an addiction medicine specialist is recommended when appropriate (Litwin, 2009); (Strathdee, 2005).

People with acute hepatitis C are often asymptomatic or have nonspecific symptoms (eg, fatigue, anorexia, mild or moderate abdominal pain, low-grade fever, nausea, and/or vomiting) that frequently are not recognized as being associated with acute HCV infection. A small proportion (<25%) of persons with acute HCV infection develop jaundice. People diagnosed with acute HCV infection should initially be monitored with hepatic panels (ALT, aspartate aminotransferase [AST], bilirubin, and international normalized ratio [INR] in the setting of an increasing bilirubin level) at 2-week to 4-week intervals (Blackard, 2008). With treatment, a rapid improvement of hepatic laboratory parameters is expected.

There is no need to alter concomitant medications that are metabolized by hepatic enzymes unless there is concern for developing acute liver failure (eg, increasing bilirubin level and INR). Acetaminophen and alcohol consumption should be avoided during acute HCV infection (Curry, 2018); (Proeschold-Bell, 2012); (Dieperink, 2010);.

Hospitalization is rarely indicated unless nausea and vomiting are severe. Although acute liver failure is exceedingly rare (<1%), it represents a serious and life-threatening complication of acute HCV infection. Persons with an INR >1.5 and those who exhibit any signs of acute liver failure (eg, hepatic encephalopathy) should be referred to a liver transplant center immediately. Use of HCV antiviral regimens in acute liver failure should be managed by a clinician experienced in HCV treatment, ideally in consultation with a liver transplant specialist.

HCV infection spontaneously clears in 20% to 50% of people (Grebely, 2014); (Kamal, 2008). Clearance of acute HCV infection occurs within 6 months of the estimated time of infection (median, 16.5 weeks) in at least two-thirds of persons who spontaneously clear HCV infection. Only 11% of those who remain viremic at 6 months will spontaneously clear the infection at a later time (Grebely, 2014). People who have spontaneously cleared HCV infection should not be treated with antiviral therapy. However, they should be counseled about the possibility of reinfection and tested routinely for this development if risk behaviors are ongoing (see Testing and Linkage to Care). Of note, transient suppression of viremia can occur in those with acute HCV infection, even among those who progress to chronic infection. Thus, a single undetectable HCV RNA test result is insufficient to declare spontaneous clearance (see Testing and Linkage to Care) (Mosley, 2008); (Villano, 1999).

Predictors of spontaneous clearance include jaundice, elevated ALT level, hepatitis B virus surface antigen (HBsAg) positivity, female sex, younger age, genotype 1 infection, and host genetic polymorphisms, most notably those near the IL28B gene (Kamal, 2008); (Mosley, 2008).

Antiviral Therapy

Recommended Regimens for Persons With Acute HCV Infection	
RECOMMENDED	RATING
Owing to high efficacy and safety, the same regimens that are recommended for chronic HCV infection are recommended for acute infection.	IIa, C

A number of studies have evaluated DAA treatment of acute HCV infection. Small single-arm, uncontrolled studies have evaluated 6 weeks or 8 weeks of ledipasvir/sofosbuvir. One such study demonstrated a 100% SVR rate with 8 weeks of ledipasvir/sofosbuvir among 27 men with acute HCV infection and HIV

coinfection (Naggie, 2019). Investigators conducting another study evaluated 6 weeks of ledipasvir/sofosbuvir in a similar cohort (25/26 with HIV coinfection). Among participants with genotype 1 infection, 79% (15/19) achieved SVR12; 71% (5/7) of those with genotype 4 infection attained SVR12 with this shortened regimen. Among the 6 individuals whose treatment did not lead to SVR12, there were 3 relapses; all had baseline HCV RNA levels >7 $\log_{10}$ IU/mL. Three participants achieved SVR4 but were lost to follow-up (Rockstroh, 2017b). A phase 2 study evaluating 6 weeks of ledipasvir/sofosbuvir among 20 individuals with genotype 1 HCV monoinfection, all of whom attained SVR12 (Deterding, 2017).

An open-label, single-arm, multicenter pilot study evaluated the efficacy of 6 weeks of the pangenotypic regimen glecaprevir/pibrentasvir among persons with acute/recent HCV infection (ie, duration of infection <12 months). SVR12 rate was 90% (27/30); a single virological failure occurred in a person with genotype 1a infection, HIV coinfection, and a viral load of 7.7 $\log_{10}$ IU/mL. This individual was successfully retreated (Martinello, 2020). Another open-label, single-arm, multicenter trial evaluated the efficacy of 4 weeks of daily glecaprevir/pibrentasvir among 23 adults with recent HCV infection (duration of infection <12 months or antibody seroconversion within 18 months). Ninety-six percent of the study population were men; 70% had HIV coinfection and 74% had genotype 1a infection. SVR12 was attained by 78% (18/23) of participants. Notably, the SVR12 rate among those with baseline HCV RNA ≤6 $\log_{10}$ was 100% (12/12). No serious adverse events were reported. Four participants relapsed; 3 were retreated. Two retreated participants attained SVR12 and the third was lost to follow-up (Martinello, 2023). Although the majority of participants in these small studies evaluating abbreviated courses of glecaprevir/pibrentasvir attained SVR, the SVR rates were lower than those seen with the longer recommended duration of treatment (≥8 weeks).

In the only randomized trial to date, investigators compared 6 weeks versus 12 weeks of sofosbuvir/velpatasvir in the international REACT trial of acute/recent HCV infection. The study was stopped early due to inferiority of the shortened duration of therapy arm (ie, 6 weeks). In the 6-week arm, SVR rates in the intention-to-treat and modified intention-to-treat analyses were 81.7% (76/93) and 89.4% (76/85), respectively. There were 6 relapses and 8 nonvirologic failures in the 6-week study arm. In the 12-week study group, SVR rates in the intention-to-treat and modified intention-to-treat analyses were 90.5% (86/95) and 97.7% (86/88) with no virologic failures. Three participants were lost to follow-up. There were no clear predictors of relapse aside from shorter treatment duration (Matthews, 2021).

To date, there are insufficient data to support a particular regimen or treatment duration outside of a clinical trial. Until more definitive data are available, treatment as described for chronic hepatitis C is recommended (see Initial Treatment of HCV Infection) for persons with acute HCV infection. Pangenotypic regimens are recommended if HCV genotyping is unavailable or if concern of exposure to more than 1 genotype exists. Using the same regimens to treat acute/recent HCV as for chronic HCV infection also simplifies management, as defining acute HCV infection may be clinically challenging.

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Additional Reading

- Initial Treatment of Adults with HCV Infection

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