Management of Acute HCV Infection

This section provides guidance on the diagnosis and medical management of acute HCV infection, which is defined as presenting within 6 months of the exposure. During this time, there is a 20% to 50% chance of spontaneous resolution of infection (Kamal, 2008). In the past, cure rates of acute infection with IFN-based treatment were very high (Grebely, 2014). The present guidance reflects current trends transitioning toward safer, IFN-sparing treatments for chronic infection and the implications for the approach to acute HCV treatment.

Acute HCV infection may result from exposure to the virus through various routes. The highest risk is associated with repeated parenteral exposures from contaminated equipment in an injection drug use (IDU) setting. Lower rates of HCV transmission occur from needlestick injuries in which healthcare workers are exposed to the blood of an HCV-infected patient. Heterosexual exposure risk is very low. In comparison, transmission rates among HIV-infected men who have unprotected sex with men are much higher, particularly among those who engage in high-risk sexual practices that increase trauma to the mucosal membranes and exposure to blood (Boesecke, 2012).

Recommended Testing for Diagnosing Acute HCV Infection	
RECOMMENDED	RATING
HCV antibody and HCV RNA testing are recommended when acute HCV infection is suspected due to exposure, clinical presentation, or elevated aminotransferase levels (see Figure).	I, C

Recommendations for HCV testing are also found in the HCV Testing and Linkage to Care section.

Diagnosis of acute infection permits 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 transmission of the virus and progression of liver disease (Bruneau, 2014). Indeed, some persons involved in high-risk behaviors practice serosorting, defined as using anti-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 (1) a positive HCV RNA test in the setting of a negative HCV antibody test (identification during the seronegative “window” period) (Cox, 2005), or (2) a positive HCV antibody test after prior negative HCV antibody test (termed 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 above types of clear laboratory documentation of acute infection are easiest to achieve when there has been a discrete exposure (eg, after new onset or a change in drug injection practice, a percutaneous needlestick exposure to an HCV-infected individual, a potentially nonsterile tattoo, or sexual assault). In those instances, baseline HCV antibody and RNA testing should be done within 48 hours of the exposure to document whether there was antecedent HCV infection (see 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 anti-HCV antibody testing is positive but RNA testing is negative, repeat HCV RNA and alanine aminotransferase (ALT) testing is recommended to identify an acute reinfection. When baseline HCV antibody and RNA testing are both positive, the person most likely already has chronic HCV infection from prior exposures. The frequency of repeat testing should reflect management goals.

At a minimum, repeat testing should be done 4 months to 6 months later. When earlier identification of infection or reinfection is desired, HCV RNA and ALT testing every 4 weeks to 6 weeks for 6 months is recommended.

No Discrete Exposure

Often, individuals suspected of having acute HCV infection do not have a discrete exposure or have no prior baseline testing, making a diagnosis of acute infection more difficult (see Table below). Acute infection should be suspected if there is a new rise in the ALT level without an alternate cause (Blackard, 2008); (Kim, 2013). Acute infection should also be suspected when there are low (especially $<10^4$ IU/mL) or fluctuating (>1 $\log_{10}$ IU/mL) HCV RNA values, or spontaneous clearance, which do not commonly occur outside of the first 6 months after acute HCV infection (McGovern, 2009). A low signal-to-cutoff ratio of HCV antibody along with detectable HCV RNA may also be suggestive of the early weeks of acute primary infection, although this information may need to be specifically requested from the testing laboratory (Araujo, 2011). Patients 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, HDV if chronically infected with hepatitis B [Kushner, 2015], or autoimmune hepatitis) and should be tested for HIV.

Not Recommended	
NOT RECOMMENDED	RATING
Preexposure or postexposure prophylaxis with antiviral therapy is Not Recommended	III, C

Although new antiviral treatment regimens are highly efficacious and more tolerable than IFN-based therapy, there are no data on the efficacy or cost-effectiveness of antiviral therapy for preexposure or postexposure prophylaxis of HCV infection. Some studies have shown that postexposure treatment with IFN-based regimens does not prevent infection (Nakano, 1995); (Arai, 1996).

Table. Interpretation of Blood Testing During Diagnosis of Acute HCV Infection

Test	Interpretation for Diagnosis of Acute HCV Infection
HCV antibody	• May be negative in the first 6 weeks after exposure • May be delayed or absent when the individual is immunosuppressed • Presence alone does not distinguish between acute and chronic infection • Low signal-to-cutoff ratio may be present during acute HCV infection or represent a false-positive result
HCV RNA	• Viral fluctuations greater than 1 $\log_{10}$ IU/mL may indicate acute HCV infection • May be transiently negative during acute HCV infection • Alone does not distinguish between acute and chronic infection
Alanine amino transferase (ALT)	• Fluctuating peaks during acute HCV infection suggest acute infection • May be normal during acute HCV infection • May be elevated due to other liver insults such as alcohol consumption

Recommendations for Medical Management and Monitoring in Acute HCV Infection

RECOMMENDED	RATING
Regular laboratory monitoring is recommended in the setting of acute HCV infection. Monitoring HCV RNA (eg, every 4 weeks to 8 weeks) for 6 months to 12 months is also recommended to determine spontaneous clearance of HCV infection versus persistence of infection.	I, B
Counseling is recommended for patients 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 patients with acute HCV infection related to substance use.	I, B

The patient with acute HCV infection should be counseled to reduce behaviors that could result in transmission, such as sharing of injection equipment or high-risk sexual practices. Because the risk of transmission of other infections is higher in the acute infection phase, some experts counsel patients with acute infection to consider using barrier precautions even in stable monogamous relationships (see HCV Testing and Linkage to Care). For individuals with acute HCV infection who have a history of recent injection drug use, referral to an addiction medicine specialist is recommended when appropriate (Litwin, 2009); (Strathdee, 2005).

Patients with acute HCV infection are often asymptomatic or have nonspecific symptoms (fatigue, anorexia, mild or moderate abdominal pain, low-grade fever, nausea, vomiting) that frequently are not recognized as being associated with acute HCV infection. A small proportion (<25%) of patients with acute HCV infection will develop jaundice. Patients diagnosed with acute HCV infection should be initially monitored with hepatic panels (ALT, aspartate aminotransferase [AST], bilirubin, and international normalized ratio [INR] in the setting of increasing bilirubin level) at 2- to 4-week intervals (Blackard, 2008). Laboratory monitoring should continue until the ALT levels normalize and HCV RNA becomes repeatedly undetectable, suggesting spontaneous resolution. If this does not occur, frequency of laboratory monitoring for patients with persistently detectable HCV RNA and elevated ALT levels should follow recommendations for monitoring patients with chronic HCV infection (see Monitoring Patients Who Are Starting Hepatitis C Treatment, Are on Treatment, or Have Completed Therapy).

HCV infection will spontaneously clear in 20% to 50% of patients (Kamal, 2008). In at least two-thirds of patients, this will occur within 6 months of the estimated time of infection (median, 16.5 weeks); only 11% of those who remain viremic at 6 months will spontaneously clear infection at some later time (Grebely, 2014). Thus, detectable HCV RNA at 6 months after the time of infection will identify most persons who need HCV therapy (see When and in Whom to Initiate HCV Therapy). Those with spontaneous clearance should not be treated with antiviral therapy, but they should be counseled about the possibility of reinfection and tested routinely for reinfection if risk behaviors are ongoing (see HCV Testing and Linkage to Care). Of note, transient suppression of viremia can occur in those with acute HCV infection, even in those who progress to chronic infection. Thus, a single undetectable HCV RNA value is insufficient to declare spontaneous clearance (Villano, 1999); (Mosley, 2008) (see HCV Testing and Linkage to Care).

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

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 (Proeschold-Bell, 2012); (Dieperink, 2010); (Whitlock, 2004). Hospitalization is rarely indicated unless nausea and vomiting are severe. Although acute liver failure is very rare (<1%), it represents a serious

and life-threatening complication of acute HCV infection. Patients with an INR above 1.5 or those who exhibit any signs of acute liver failure (eg, hepatic encephalopathy) should be referred to a liver transplant center immediately. The 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.

Recommended Treatment for Patients with Acute HCV Infection

RECOMMENDED	RATING
If the practitioner and patient have decided that a delay in treatment initiation is acceptable, monitoring for spontaneous clearance is recommended for a minimum of 6 months. When the decision is made to initiate treatment after 6 months, treating as described for chronic hepatitis C is recommended (see Initial Treatment of HCV Infection).	IIa, C
If a decision has been made to initiate treatment during the acute infection period, monitoring HCV RNA for at least 12 weeks to 16 weeks before starting treatment is recommended to allow for spontaneous clearance.	IIa, C

Recommended Regimens for Patients 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

Not Recommended

NOT RECOMMENDED	RATING
For patients in whom HCV infection spontaneously clears, treatment is Not Recommended.	III, B

In the interferon era, the efficacy of the treatment of acute HCV infection (particularly for genotype 1), including with abbreviated regimens, was superior to the treatment of chronic infection (See 2009 AASLD guidelines [Ghany, 2009]). There are emerging data on the treatment of acute HCV infection with shortened courses of all-oral DAA regimens both in HCV monoinfection and HIV/HCV coinfection, but there are, as yet, not enough data to support a particular regimen or duration. Until more definitive data are available, monitoring for spontaneous clearance for a minimum of 6 months before initiating treatment is recommended. When the decision is made to initiate treatment after 6 months, treatment as described for chronic hepatitis C is recommended.

There are instances, however, where clinicians may decide that the benefits of early treatment outweigh waiting for HCV clearance. These include situations where importance is placed on the prevention of HCV transmission (eg, surgeon, IVDU, and or HIV+ MSM with sexual transmission), mitigation of clinical consequences (eg, patient with cirrhosis who is acutely superinfected with HCV), or reduction in likelihood of loss-to-follow-up in patients who may not be engaged in care in 3-to-6 months. Where relevant, referral to addiction specialists and harm reduction counseling should be provided. If for these reasons a decision has been made to initiate treatment during the acute infection period, the same regimens recommended for chronic HCV infection (see Initial Treatment of HCV Infection and When and in Whom to Initiate HCV Therapy sections) are recommended for acute infection given their high efficacy and safety in chronic HCV infection.

Mixed genotypes

Rarely, genotyping assays may indicate the presence of a mixed infection (eg, genotypes 1a and 2). Treatment data for mixed genotypes with direct-acting antivirals are sparse but utilization of a pangenotypic regimen should be considered. When the correct combination or duration is unclear, expert consultation should be sought.

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