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 period, there is a 20% to 50% chance of spontaneous resolution of the infection (Kamal, 2008). In the past, cure rates of acute infection with interferon-based treatment were very high (Grebely, 2014). The present guidance reflects current trends transitioning toward safer, interferon-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 exposure from contaminated equipment in an injection drug use setting. Lower rates of HCV transmission occur from needle-stick injuries in which healthcare workers are exposed to the blood of an HCV-infected patient. Heterosexual exposure risk is very low. 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).

Diagnosis of Acute HCV

Recommended Testing for Diagnosing Acute HCV Infection

<table>
<thead>
<tr>
<th>RECOMMENDED</th>
<th>RATING</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCV antibody and HCV RNA testing are recommended when acute HCV infection is suspected due to exposure, clinical presentation, or elevated aminotransferase levels (see Testing Algorithm figure).</td>
<td>I, C</td>
</tr>
</tbody>
</table>

Recommended for HCV testing are also found in the HCV 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). Indeed, 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: (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 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 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 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 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 exposure(s). The frequency of repeat testing should reflect management goals. At a minimum, repeat testing should be done 4 to 6 months after baseline testing. When earlier identification of infection or reinfection is desired, HCV RNA and ALT testing every 4 to 6 weeks for 6 months is recommended.

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 alternate cause (Blackard, 2008); (Kim, 2013). Acute infection should also be suspected when there are low (especially <10^4 IU/mL) or fluctuating (>1 log10 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). A low signal-to-cutoff ratio of HCV antibody along with detectable HCV RNA might 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, hepatitis delta virus if chronically infected with hepatitis B, and autoimmune hepatitis) (Kushner, 2015). Patients should also have HIV testing.

Table. Interpretation of Blood Tests for Diagnosis of Acute HCV Infection

<table>
<thead>
<tr>
<th>TEST</th>
<th>INTERPRETATION FOR DIAGNOSIS OF ACUTE HCV</th>
</tr>
</thead>
</table>
| HCV Antibody | - Test may be negative during the first 6 weeks after exposure.  
              - Seroconversion may be delayed or absent in immunosuppressed individuals.  
              - Presence of HCV antibody alone does not distinguish between acute vs chronic infection.  
              - A low signal-to-cutoff ratio may be present during acute HCV infection or represent a false-positive result. |
| HCV RNA    | - Viral fluctuations >1 log10 IU/mL may indicate acute HCV infection.  
              - HCV RNA may be transiently negative during acute HCV infection.  
              - Presence of HCV RNA alone does not distinguish between acute vs 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. |
Pharmacologic Prophylaxis

Pharmacologic Prophylaxis Not Recommended

<table>
<thead>
<tr>
<th>NOT RECOMMENDED</th>
<th>RATING</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-exposure or post-exposure prophylaxis with antiviral therapy is not recommended.</td>
<td>III, C</td>
</tr>
</tbody>
</table>

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

* Repeat HCV Ab is not needed if it is positive at baseline. Frequency of testing can be tailored based on management objectives (eg, monthly testing to identify and treat acute infection).

* Some would treat after waiting 8 weeks to 12 weeks for spontaneous clearance (see text). Benefits of HCV antiviral therapy or IFN-based (alternative) within 12 weeks of acute infection are that this may decrease transmission risk to others (eg, among injection drug users or surgeons), prevent severe complications (eg, underlying cirrhosis superinfected with acute HCV infection), and minimize chance of being lost to follow-up.

* 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 help distinguish acute from chronic HCV.

* Baseline testing should be done within 48 hours of exposure to determine existing infection status: HCV RNA, HCV Ab, and ALT.
Although direct-acting antiviral (DAA) treatment regimens are highly efficacious and more tolerable than interferon-based therapy, there are no data on the efficacy or cost effectiveness of antiviral therapy for pre-exposure or post-exposure prophylaxis of HCV infection. Some studies have shown that post-exposure treatment with an interferon-based regimen does not prevent infection (Nakano, 1995; Arai, 1996).

### Medical Management and Monitoring of Acute HCV Infection

#### Recommendations for Medical Management and Monitoring of Acute HCV Infection

<table>
<thead>
<tr>
<th>RECOMMENDED</th>
<th>RATING</th>
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</thead>
<tbody>
<tr>
<td>Regular laboratory monitoring is recommended in the setting of acute HCV infection. Monitoring HCV RNA (eg, every 4 to 8 weeks) for 6 to 12 months is also recommended to determine spontaneous clearance versus persistence of HCV infection.</td>
<td>I, B</td>
</tr>
<tr>
<td>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.</td>
<td>I, C</td>
</tr>
<tr>
<td>Referral to an addiction medicine specialist is recommended for patients with acute HCV infection related to substance use.</td>
<td>I, B</td>
</tr>
</tbody>
</table>

Patients with acute HCV infection should be counseled to reduce behaviors that could result in virus transmission, such as sharing of injection equipment and 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 patients with acute HCV to consider using barrier precautions, even in a stable monogamous relationship (see HCV Testing and Linkage to Care). For individuals with acute HCV 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 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 patients with acute HCV develop jaundice. Patients diagnosed with acute HCV should be initially monitored with hepatic panels (ALT, aspartate aminotransferase [AST], bilirubin, and international normalized ratio [INR] in the setting of an increasing bilirubin level) at 2- to 4-week intervals (Blackard, 2008). Laboratory monitoring should continue until the ALT level normalizes 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 spontaneously clears in 20% to 50% of patients (Kamal, 2008). In at least two-thirds of patients who spontaneous clear acute HCV infection, this occurs 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 the infection at a later time (Grebely, 2014). Thus, detectable HCV RNA at 6 months after the time of infection will identify most persons who need antiviral
therapy (see When and in Whom to Initiate HCV Therapy).

Patients who spontaneous clear should not be treated with antiviral therapy. However, 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 among those who progress to chronic infection. Thus, a single undetectable HCV RNA test result is insufficient to declare spontaneous clearance (see HCV Testing and Linkage to Care); (Villano, 1999); (Mosley, 2008).

Predictors of spontaneous clearance include jaundice, elevated ALT level, hepatitis B virus surface antigen (HBsAg) positivity, female sex, younger age, HCV genotype 1 infection, 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 >1.5 and 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.

Antiviral Therapy

Recommended Treatment for Patients With Acute HCV Infection

<table>
<thead>
<tr>
<th>RECOMMENDED</th>
<th>RATING</th>
</tr>
</thead>
<tbody>
<tr>
<td>If the clinician and patient decide 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).</td>
<td>Ila, C</td>
</tr>
<tr>
<td>If a decision is made to initiate treatment during the acute infection period, monitoring HCV RNA for at least 12 to 16 weeks before starting treatment is recommended to allow time for possible spontaneous clearance.</td>
<td>Ila, C</td>
</tr>
</tbody>
</table>

Recommended Regimens for Patients With Acute HCV Infection

<table>
<thead>
<tr>
<th>RECOMMENDED</th>
<th>RATING</th>
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</thead>
<tbody>
<tr>
<td>Owing to high efficacy and safety, the same regimens that are recommended for chronic HCV infection are recommended for acute infection.</td>
<td>Ila, C</td>
</tr>
</tbody>
</table>

When Antiviral Therapy Is Not Recommended

<table>
<thead>
<tr>
<th>NOT RECOMMENDED</th>
<th>RATING</th>
</tr>
</thead>
<tbody>
<tr>
<td>For patients in whom HCV infection spontaneously clears, antiviral treatment is not recommended.</td>
<td>III, B</td>
</tr>
</tbody>
</table>
In the interferon era, the efficacy of acute HCV infection treatment (particularly for genotype 1), including 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 as yet, there are insufficient data to support a particular regimen or treatment 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 antiviral therapy after 6 months, treatment as described for chronic hepatitis C is recommended (see Initial Treatment of HCV Infection and When and in Whom to Initiate HCV Therapy).

There are instances wherein a clinician may decide that the benefits of early treatment outweigh waiting for possible spontaneous clearance. These include situations where importance is placed on:

- HCV transmission prevention (eg, a surgeon, a person with ongoing intravenous drug use, or an HIV-positive man who engages in sex with other men)
- Mitigation of clinical consequences (eg, a patient with cirrhosis who is acutely superinfected with HCV)
- Reduction in the likelihood of loss to follow-up (eg, a patient who may not be engaged in care in 3 to 6 months)

Referral to an addiction specialist and harm reduction counseling should be provided if relevant. If a decision is made to initiate treatment during the acute infection period, the same regimens recommended for chronic HCV infection are recommended for acute infection, given their high efficacy and safety in chronic HCV infection (see Initial Treatment of HCV Infection and When and in Whom to Initiate HCV Therapy sections).

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