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).

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).

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 and algorithm 4 and algorithm 5) (**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.)

SUMMARY AND RECOMMENDATIONS

- **Rationale** – Hepatitis C virus (HCV) infection is a global health problem that can progress to cirrhosis and end-stage liver disease in a substantial proportion of patients. Because it is frequently asymptomatic, screening is essential to improving detection and ultimately treatment of infected individuals. (See 'Rationale' above.)

- **Universal one-time screening** – We suggest one-time screening for HCV infection in all adults ≥18 years of age rather than selective screening (**Grade 2C**). This recommendation is supported by the substantial individual benefit of treatment of HCV infection, the minimal harms of screening, and the limitations of risk-based screening in identifying patients with infection. (See 'Routine one-time screening for adults' above.)

- **Selective repeat screening** – Repeat screening is warranted for patients who have ongoing risk of exposure (eg, people who use injection drugs, patients on chronic hemodialysis, men who have sex with men who have HIV or are using pre-exposure prophylaxis to prevent HIV, and long-term sex partners of individuals with HCV infection) and for pregnant individuals during each pregnancy. (See 'Repeat screening for select individuals' above.)

- **Testing for clinical suspicion** – Testing for HCV infection is also warranted in people with evidence of liver disease, with extrahepatic conditions associated with HCV (eg, porphyria cutanea tarda, mixed cryoglobulinemia), or with known exposure. (See 'Patients with consistent clinical features' above and 'Very recent exposure' above.)

- **Diagnosis** – The diagnosis of chronic HCV infection is usually made in a patient with a reactive HCV antibody test and a positive molecular test that detects the presence of HCV RNA (algorithm 1). Usually, patients who have both reactive anti-HCV antibody and detectable HCV RNA have chronic infection, although these may also be seen in some acutely infected patients. (See 'Diagnosis' above.)

- **Initial antibody test** – Initial screening or diagnostic testing for chronic HCV typically begins with an antibody test (ideally with a reflex HCV RNA test). (See 'Standard approach' above.)

- **Nonreactive antibody test** – For most people, chronic HCV infection is unlikely with a nonreactive antibody test, and testing can stop. Patients who are on hemodialysis, are severely immunocompromised, or are suspected of having an acute HCV infection may not have detectable anti-HCV antibodies despite the presence of infection; in such patients, HCV RNA testing despite a nonreactive antibody test is important to exclude infection. (See 'Nonreactive anti-HCV antibody' above.)

- **Reactive antibody test** – This should be followed with an HCV RNA test. The absence of detectable HCV RNA using a sensitive assay essentially confirms the absence of chronic HCV infection. False-negative tests for RNA are unusual. A reactive antibody test in this setting is generally a false positive or reflective of past, cleared infection. A positive HCV RNA result is evidence of HCV infection. (See 'Reactive antibody and negative RNA test' above and 'Reactive antibody and positive RNA test' above.)

A diagnostic approach to suspected acute hepatitis C is presented separately. (See "Clinical manifestations, diagnosis, and treatment of acute hepatitis C virus infection in adults", section on 'Diagnosis'.)

- **Diagnostic techniques** – Antibodies to HCV can be detected using a number of assays, including standard immunoassays that are performed in a laboratory, rapid immunoassays that can be performed at the point of care, and home tests on specimens self-collected by the patient. Nucleic acid tests for detection of HCV RNA have been traditionally divided into two categories: qualitative and quantitative assays. Most currently available quantitative tests have a lower level of detection that is comparable to qualitative tests. (See 'Diagnostic techniques' above.)

- **Postdiagnostic evaluation** – Important aspects of initial care of the patient newly diagnosed with HCV involve evaluating the extent of liver damage and assessing factors that inform treatment decisions. These are discussed in detail elsewhere. (See "Patient evaluation and selection for antiviral therapy for chronic hepatitis C virus infection", section on 'Evaluation'.)

Overview of the management of chronic hepatitis C virus infection

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INTRODUCTION

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

GENERAL MANAGEMENT

Antiviral therapy is the cornerstone of treatment of chronic hepatitis C virus (HCV) infection (see 'Antiviral therapy' below). With current antiviral therapies, HCV is relatively easily treated and can be eliminated in almost all patients. Other general measures in the management of patients with chronic HCV include symptom management, dose adjustment of medications, and preventing complications of cirrhosis if present.

Fatigue — Many patients with HCV infection complain of fatigue. The cause is uncertain and may be difficult to ascribe to liver disease alone rather than other comorbidities such as depression. Fatigue and overall quality of life improve in some patients who have a sustained virologic response (SVR) following antiviral therapy, although the improvements may be modest [7,8]. (See "Patient evaluation and selection for antiviral therapy for chronic hepatitis C virus infection", section on 'Symptom alleviation'.)

ANTIVIRAL THERAPY

Goals of therapy — The goal of antiviral therapy in patients with chronic hepatitis C virus (HCV) is to eradicate HCV RNA, which is predicted by attainment of a sustained virologic response (SVR), defined as an undetectable RNA level 12 weeks following the completion of therapy.

An SVR is associated with a 97 to 100 percent chance of being HCV RNA negative during long-term follow-up and can therefore be considered cure of the HCV infection [16]. Attaining an SVR (with direct-acting antiviral [DAA] regimens as well as with interferon-based regimens) has been associated with decreases in all-cause mortality, liver-related death, need for liver transplantation, hepatocellular carcinoma rates, and liver-related complications, even among those patients with advanced liver fibrosis [17-32]. (See "Patient evaluation and selection for antiviral therapy for chronic hepatitis C virus infection", section on 'Rationale for treatment'.)

SUMMARY AND RECOMMENDATIONS

- **Initial evaluation** – The evaluation of patients with chronic hepatitis C virus (HCV) infection involves assessing the extent of liver disease, assessing other viral and host factors (including viral genotype, liver fibrosis stage, history of prior antiviral treatment, renal function, and medication use) that inform optimal antiviral selection, and identifying comorbidities associated with HCV infection (including extrahepatic manifestations of HCV infection as well as human immunodeficiency virus [HIV] and hepatitis B virus [HBV] infection). (See "Screening and diagnosis of chronic hepatitis C virus infection", section on 'Additional evaluation' and "Patient evaluation and selection for antiviral therapy for chronic hepatitis C virus infection", section on 'Evaluation'.)

- **Counseling on transmission risk and dietary/behavioral modifications** – HCV-infected patients should be counseled on measures to decrease the risk of transmission (table 1) and correcting factors associated with accelerated liver disease, including alcohol use, obesity and insulin resistance, and marijuana use.

  Substance use treatment is also an important element of care in patients who have ongoing illicit drug use. (See 'Counseling' above.)

- **Additional management issues for advanced fibrosis** – Additional management is warranted for patients who are found to have advanced fibrosis or cirrhosis, including dose modification or avoidance of certain medications (table 2 and table 3), twice yearly ultrasonography for hepatocellular carcinoma screening, and upper endoscopy screening for esophageal varices. (See 'Patients with advanced liver fibrosis or cirrhosis' above and "Cirrhosis in adults: Overview of complications, general management, and prognosis", section on 'General management'.)

- **Goals and benefits of antiviral therapy** – All patients with virologic evidence of chronic HCV infection (ie, detectable HCV viral level over a six-month period) should be considered for antiviral treatment. The goal is to eradicate HCV RNA, which is associated with decreases in all-cause mortality, liver-related death, need for liver transplantation, hepatocellular carcinoma rates, and liver-related complications. (See 'Antiviral therapy' above and "Patient evaluation and selection for antiviral therapy for chronic hepatitis C virus infection".)

- **Regimen selection** – Highly effective two- to three-month oral regimens are appropriate options for the majority of individuals with chronic HCV infection. Pan-genotypic regimens are generally first-line options. Regimen selection is presented by genotype and depends on treatment history and other patient factors. (algorithm 1 and algorithm 2 and algorithm 3 and algorithm 4). (See "Treatment regimens for chronic hepatitis C virus genotype 1 infection in adults" and "Treatment regimens for chronic hepatitis C virus genotypes 2 and 3 infection in adults" and "Treatment regimens for chronic hepatitis C virus genotypes 4, 5, and 6 infection in adults".)

- **Monitoring during treatment** – It is important to emphasize the importance of adherence at each clinic visit. Intermittent laboratory monitoring may be warranted for certain regimens and for patients with evidence of prior or current HBV infection. The purpose of viral level monitoring during treatment is primarily to assess adherence and document the treatment course. We typically check a quantitative HCV RNA test at week 4 of therapy. (See 'Interferon-free regimens' above.)

- **Assessment of treatment success** – Virologic response to treatment should be assessed by checking the viral load at 12 weeks following the cessation of therapy. Sustained virologic response (SVR) is defined by an undetectable viral level at this time point. (See 'Follow-up after antiviral therapy' above.)

- **Post-treatment management** – Patients who fail to achieve an SVR should continue to be followed for signs of progression of liver disease and assessed for retreatment of HCV infection. Patients with advanced fibrosis or cirrhosis, regardless of whether they attain an SVR, warrant ongoing monitoring because they continue to be at risk of hepatocellular carcinoma and other complications. (See 'Follow-up after antiviral therapy' above.)