Initial Evaluation of Persons with Chronic Hepatitis C

Key Aspects of Medical History

Confirming Diagnosis of Hepatitis C Infection: The initial hepatitis C evaluation may involve a person newly diagnosed with hepatitis C infection, or an individual previously diagnosed with hepatitis C who is establishing or reestablishing clinical care for their hepatitis C infection. First, the clinician should review the hepatitis C test results and confirm the patient has chronic hepatitis C virus (HCV) infection and not resolved HCV.

General Approach to Initial Evaluation: During the initial evaluation, the clinician should perform a thorough history and physical examination, focusing particularly on risk factors for acquiring HCV infection, presence of significant medical comorbidities, psychiatric history, coinfection with other viruses, stigmata of chronic liver disease, clinical manifestations attributable to hepatitis C infection, prior assessment of liver fibrosis, and a history of prior treatment. In addition, the initial evaluation should assess for any ongoing risk of HCV transmission, ascertain for use of alcohol or any other substance that would cause further liver toxicity, and identify barriers to treatment. Assessment of the stage of liver disease is a complex task and should be addressed in subsequent follow-up visits.

Identifying Risk Factors for HCV Acquisition: Identifying an individual patient’s risk factor for HCV acquisition is important in order to properly counsel the patient regarding risk of onward transmission and prevention of re-infection. In the United States, the major risk factors for HCV acquisition are injection drug use (IDU), receipt of a blood transfusion or organ transplant prior to 1992, exposure to an infected sexual partner, occupational needlestick injury, tattooing, and mother-to-child transmission. Recently, there has been recognition of a sexually transmitted hepatitis C epidemic among men who have sex with men (MSM), particularly men with HIV infection. Some individuals may not disclose a possible risk factor for acquiring hepatitis C at the initial visit and when this occurs the clinician should readdress this issue at a later point after they have hopefully established a good rapport with the patient. The reluctance to disclose risk of HCV acquisition is particularly common in individuals who have a remote history of injection drug use.

Alcohol History: Determining the presence of current and prior alcohol is important for two major reasons. First, the ongoing alcohol intake of even moderate amounts (50 g/day or more) leads to ongoing hepatotoxicity and accelerated progression of liver fibrosis. Second, even in the interferon-free era, ongoing heavy alcohol use can be a major barrier to treatment of HCV. Because denial is often intertwined with chronic ethanol use, obtaining an accurate history can be difficult. Several well-validated tools are recommended for alcohol abuse screening, including the CAGE Questionnaire, a 4-question screening tool (Figure 1), and the Alcohol Use Disorders Identification Test (AUDIT). The AUDIT-C is a 3-question modified version of the 10-question AUDIT screening instrument and a more practical tool than the AUDIT in clinical settings (Figure 2). No consensus opinion exists regarding treatment of individuals with a history of alcohol abuse who have ongoing infrequent alcohol consumption, but many HCV-treating clinics use a minimum criterion of 6 months of sobriety.
as a general measure of readiness for therapy.

**Injection Drug Use History:** For patients with a history of past or present injection-drug use, it is important to assess whether they have active drug use or are likely to use again in the future. Asking about injection-drug use may aid in determining the initial mode of infection, which informs further screening for co-infections, such as HIV and hepatitis B virus. In addition, it is also helpful to determine the age of first drug use, since this may give insight into the likely duration of HCV infection, which in turn may provide indirect evidence for severity of liver disease. Individuals with active injection-drug use should receive counseling on safe injection practices to prevent onward transmission of HCV, and should be offered appropriate treatment and support towards abstinence. Ongoing active injection-drug use is not an absolute contraindication to treatment of hepatitis C, but it can impact the complex decision to treat, mainly due to potential difficulty in adhering to treatment and risk for re-infection with HCV.

**Psychiatric History:** Patients with HCV infection have a higher incidence of psychiatric illness compared with the general population, and comorbid, inadequately treated psychiatric illness represented a major barrier to successful HCV treatment in the interferon era. Interferon-based therapies for HCV have important neuropsychiatric side effects, such as depression, irritability, mood swings, and suicidality. New direct acting antivirals do cause neuropsychiatric adverse effects. In the modern treatment era, psychiatric issues take on less importance, but may still be a barrier to care with regard to linkage to care, adherence, and substance abuse.

**Presence of Medical Comorbidities:** When evaluating the patient with hepatitis C infection, the clinician should consider secondary causes of liver disease, such as non-alcoholic fatty liver disease (NAFLD), alcoholic hepatitis, or autoimmune hepatitis. Obesity and insulin resistance have been associated with inferior hepatitis C treatment responses. Guidelines advise the clinician to counsel those who are overweight (defined as Body Mass Index [BMI] greater than 25 kg/m$^2$) to attempt to lose weight prior to initiating treatment. The calculation of the patient’s BMI is based on the patient’s weight (pounds) and height (inches) ([Figure 3](#)). The National Heart, Lung, and Blood Institute has an [BMI Calculator](#) and [BMI Tables](#) for interpreting the calculated result. Congestive heart failure, anemia, psychiatric disease, renal insufficiency, thyroid disease, or autoimmune conditions are relative contraindications to receiving interferon-based therapy for HCV and thus are important to identify. Ribavirin is absolutely contraindicated in pregnant women and their male partners.

**Presence of Significant Coinfections:** Every newly diagnosed patient should undergo screening for a history of hepatitis A virus (HAV), hepatitis B virus (HBV), and human immunodeficiency virus (HIV). Coinfection with either HBV or HIV is known to accelerate the rate of hepatic fibrosis, and acute HAV in a patient with HCV can lead to fulminant hepatic failure. In the absence of immunity to HAV and HBV, immunization should be offered.

**Prior Staging of Liver Fibrosis:** For persons previously engaged in clinical care for their hepatitis C infection, it is important to determine whether they have had a liver biopsy. If so, the date of the biopsy, sample size, and fibrosis scoring system, and fibrosis score should be recorded in the medical record. In addition, the clinician should note any prior evaluation for liver fibrosis using a non-invasive method, such as hepatic ultrasound, transient elastography, serum-based Aspartate aminotransferase-to-Platelet Ratio Index (APRI), and FibroTest.

**Complications of Liver Disease:** Upon initial evaluation, it is important to determine whether the patient has already experienced complications of advanced liver disease. Treatment of HCV in cirrhotic patients is complex, and may require referral or consultation with a provider who has expertise in hepatology. The clinician should inquire about prior hospital admissions for ascites, hepatic encephalopathy, jaundice, or gastrointestinal bleeding. Furthermore, untreated hepatocellular carcinoma or the presence of decompensated cirrhosis (Child-Turcotte-Pugh class C, typically with ascites, encephalopathy, coagulopathy, or hyperbilirubinemia) indicates a need for prompt referral to a hepatologist.
Extrahepatic Clinical Manifestations Attributable to Hepatitis C Infection: Hepatitis C infection may be associated with a diverse array of extrahepatic manifestations, such as arthralgias, neuropathy, nephropathy, glomerulonephritis, livedo reticularis, lichen planus, and cold agglutinin disease. As part of the initial evaluation, the clinician should inquire about any known extrahepatic complications. In one large study, the most common symptoms in patients who had extrahepatic manifestations were arthralgia (23%), paresthesia (17%), myalgia (15%), pruritus (15%), and sicca syndrome (11%).

History of Prior Treatment for Hepatitis C: For individuals who have previously undergone unsuccessful treatment for HCV the clinician must determine the type, timing and duration of prior treatment, degree of adherence, adverse effects, and if possible, viral kinetics and outcome on treatment. Failure to achieve a sustained virologic response (SVR) occurs as a result of non-response or relapse. Non-Responders are patients who never cleared HCV from their serum during the course of treatment. Among the Non-Responders, those classified as Null Responders failed to achieve a 2-log reduction in HCV viral load after 12 weeks of therapy whereas Partial Responders are those who achieved a greater than 2-log decrease in HCV viral load at week 12 of therapy, but the HCV RNA level remained detectable at week 24 (Figure 4). Relapsers have virologic rebound after achieving an end-of-treatment response, with this usually occurring within the first 24 weeks after treatment completion (Figure 5).
Key Aspects of Physical Examination

Physical Examination of the HCV-infected Patient: During the initial evaluation visit, the clinician should ideally perform a complete physical examination, including obtaining the patient's height and weight (for determining the patient's BMI). In addition, and there are several liver-related physical findings that should be specifically sought that may identify the presence of indicators of advanced liver disease. The following is a description of some of the key physical examination findings that may indicate the presence of cirrhosis.

- **Spider nevi (angioma):** This finding results from dilated arterial blood vessels found just below the skin surface. The lesion is referred to as a "spider" nevus because of the appearance of the central arteriole that has multiple thin-walled radiating blood vessels that resemble spider legs. With direct compression on the central region of the lesion, the lesion will temporarily blanch, but with release of pressure the lesion fill back in from the center radiating outward. Typically, more than three spider nevi is considered abnormal, but this finding is not specific to liver disease.

- **Distended Abdominal Veins and Caput Medusa:** If a patient with cirrhosis develops portal hypertension, the increased pressure can cause swelling of the collateral venous channels, which may become evident as distended abdominal veins. The distended abdominal veins can radiate around the umbilicus, a finding referred to a caput medusa. On general inspection, the cirrhosis-related abdominal vein swelling can appear similar to findings with obstructions of the inferior vena cava.

- **Terry's Nails:** The initial finding of Terry's nails consists of a white-silver discoloration of the proximal nail bed, often with a pink-red transverse band on the distal edge of the discolored region. The white discoloration may progress distally to involve most of the nail bed. This finding can be distinguished from onycomycosis, since Terry's nails involves the nail bed and has a pink band, whereas onycomycosis involves the nail itself, without any pink distal band.

- **Palmar Erythema:** The finding of palmary erythema is suggested by the presence of intense erythema in the thenar and hypthenar eminence (base of the thumb and fifth finger) of the palm, with the central region of the palm spared. This finding is not specific to cirrhosis and is often seen in pregnant women.

- **Jaundice:** This term refers to a yellow discoloration of the of skin or sclera that results from excess deposition of biliary pigments. Jaundice is typically seen only when the serum bilirubin level exceeds 2.5 mg/dL. The sclera and mucous membranes under the tongue are the most sensitive sites to detect jaundice. The finding of jaundice is often an indicator of advanced liver disease and in persons with chronic liver disease strongly suggests decompensated cirrhosis. Jaundice can result from non-hepatic causes, such as hemolytic anemia.

- **Gynecomastia:** The presence of true gynecomastis refers to enlargement of the male breast glandular tissue and should be distinguished from generalized breast enlargement from fat accumulation in the breast region (lipomastia), which may be associated with obesity. Cirrhosis-related gynecomastia results from impaired hepatic degradation of estrogens, a problem enhanced if the patients with excess alcohol consumption (because of the phyoestrogens in alcohol). The finding of gynecomastia is not specific to cirrhosis.

Diagnostic Accuracy of Physical Examination Findings for Detecting Cirrhosis: Although cirrhosis is ultimately a histological diagnosis, several clinical signs and symptoms strongly suggest the presence of cirrhosis. In a meta-analysis of 86 studies, Udell and coworkers found that specific physical examination findings increase the likelihood the patient has cirrhosis, with the most frequently studied findings that had a likelihood ratio (LR) greater than 4 were distended abdominal veins, encephalopathy, ascites, and spider nevi. Although Terry nails and gynecomastia had high likelihood ratios, the confidence intervals were broad and thus harder to interpret their validity. The following is a list of the summary measures for the diagnostic accuracy of the physical examination for detecting cirrhosis, with in decreasing order of positive likelihood ratio (LR) for the presence of cirrhosis:
- Terry (white) nails (LR = 16.0-22.0)
- Gynecomastia (LR = 5.8-35.0)
- Distended abdominal veins (LR = 11.0)
- Encephalopathy (LR = 10.0)
- Decreased body hair (LR = 9.0)
- Ascites (LR = 7.2)
- Facial telangiectasia (LR = 5.9-10.0)
- Testicular atrophy (LR = 5.8)
- Palmary erythema (LR = 5.0)
- Spider nevi (LR = 4.3)
- Jaundice (LR = 3.8)
- Splenomegaly (LR = 3.5)
- Firm liver (LR = 3.3)
- Peripheral edema (LR = 3.0)
Recommended Laboratory Studies after Initial Diagnosis

Initial Laboratory Evaluation of the Patient with Chronic Hepatitis C: Although individual patient factors may demand specific testing, a core set of baseline laboratory tests are indicated for every newly diagnosed patient with HCV infection. The goal of the initial laboratory evaluation is two-fold. The clinician must both identify any abnormalities directly related to the new diagnosis of HCV, such as thrombocytopenia, liver dysfunction, or inflammation, as well as establish a broader baseline set of laboratory values to monitor during treatment (thyroid function, hemoglobin/hematocrit, renal function). The same approach holds during the initial evaluation for patients who are re-establishing medical care for their hepatitis C infection.

- **General Laboratory Evaluation**: Complete blood count (CBC), platelet count, serum creatinine, and thyroid function tests (TSH). Since several studies have shown that persons with vitamin D deficiency have reduced response to hepatitis C treatment, some experts also recommend obtaining baseline vitamin D levels (1,25-OH vitamin D).
- **Hepatic Inflammation and Function**: Alanine aminotransferase (ALT) or aspartate aminotransferase (AST), total and direct bilirubin, alkaline phosphatase, serum albumin, international normalized ratio (INR).
- **Assays to Detect Relevant Coinfections**: Hepatitis A antibody, hepatitis B surface antigen, hepatitis B core antibody, hepatitis B surface antibody, HIV antibody.
- **HCV RNA Level (“Viral Load”)**: It is important to assess a quantitative HCV RNA viral load to confirm that the patient indeed has chronic HCV infection, and also to establish a pre-treatment baseline level. In the absence of treatment, it is not necessary to repeatedly assess the HCV RNA levels, as monitoring values over time does not provide useful prognostic information.
- **HCV Genotype**: Hepatitis C virus exists as one of six distinct genotypes with markedly different clinical characteristics, mostly with respect to treatment response rates. In the United States, HCV genotype 1 is most common, accounting for 74% of prevalent cases. Determining HCV genotype is extremely important, because response to anti-viral therapy is very different among different types, and treatment protocols differ substantially.
- **IL-28B Testing**: Recently, investigators discovered a single nucleotide polymorphism (SNP) at the IL-28B locus that codes for Interferon lambda and strongly correlates with HCV treatment response. This polymorphism also explains much of the observed racial and ethnic variation in response to hepatitis C treatment. Inheritance of this gene is Mendelian, with either a C or T allele being inherited from maternal and paternal sides, respectively. Patients who are C/C homozygous typically have a greater chance of spontaneous clearance of HCV and have the best treatment response to interferon-based therapies. In select patients, this supplemental test may enrich discussions regarding the risks and benefits of pursuing therapy. Most experts would consider this test optional, at least at an initial visit.
Immunizations for Persons with Chronic HCV

**Hepatitis A Immunization:** Persons with chronic hepatitis C are more likely to have severe manifestations of acute hepatitis A infection and thus hepatitis A vaccine is recommended for all persons without immunity to hepatitis A virus. The hepatitis A immunization can be accomplished via a two-dose single antigen vaccine (*Havrix, Vaqta*) or as a 3-dose Hepatitis A/B combination vaccine (*Twinrix*) (Figure 6). Checking post-vaccination hepatitis A titers is not recommended, primarily because of the very high response to hepatitis A vaccine.

**Hepatitis B Immunization:** Similar to the recommendations for hepatitis A, all persons with chronic hepatitis C should receive hepatitis B vaccine, unless they have immunity to hepatitis B or are chronically infected with hepatitis B. The vaccine series consists of three-doses of recombinant vaccine (*Engerix-B* or *Recombivax-HB*). There is also a 3-dose Hepatitis A/B combination vaccine available (*Twinrix*) (Figure 7).

**Pneumococcal Immunization:** The Advisory Committee on Immunization practices (ACIP) recommends giving the 23-valent polysaccharide pneumococcal vaccine to all persons with alcoholism and all persons with chronic liver disease, including cirrhosis. If the individual receives the 23-valent polysaccharide pneumococcal vaccine prior to age 65, they should receive a 2nd dose at age 65 (if at least 5 years have elapsed from initial vaccine). Currently, there are no recommendations to give the conjugate pneumococcal vaccine (PCV13) to persons with alcoholism or chronic liver disease.

**Routine Adult Vaccines:** Entry into care represents an opportunity to standard adult vaccinations, such as yearly influenza and a one-time Tetanus Diphtheria Acellular Pertussis (TdAP) or Tetanus Diphtheria (Td) booster every 10 years.
Screening for other Causes and Contributors of Liver Disease

Overview of Screening for Other Causes of Liver Disease: In the course of a complete work-up of the patient infected with HCV, the clinician should make an effort to determine whether additional causes of liver disease are present, especially in cases with significant abnormalities on liver function testing. An exhaustive screening laboratory work-up for all of these conditions would be expensive and low-yield for most patients; however, they may be relevant in special situations. Therefore, the clinician should be familiar with select non-viral causes of hepatic inflammation. Other causes of liver disease may co-exist with HCV infection, including both hereditary and acquired conditions (Figure 8). Autoimmune hepatitis is an example of a secondary cause that may worsen on Interferon therapy if unrecognized.

Alcoholic Liver Disease: Ethanol is the most common cause of liver disease in the Western world, and determining intake is crucial in patients with hepatitis C infection. On a practical basis, differentiating liver injury caused by ethanol use from that due to chronic HCV infection can be difficult, but certain patterns (e.g. AST/ALT ratio of greater than 2.0) strongly suggest ethanol-related injury. In addition, screening for alcohol intake as part of the medical history may suggest alcohol as a contributor for liver disease. Ethanol can cause acute alcoholic hepatitis, fatty liver (steatosis), and eventually cirrhosis, and can accelerate HCV-associated fibrosis and hasten the onset of cirrhosis. Patients who are cured of HCV, yet continue to consume ethanol, can still progress to cirrhosis and liver failure. Given that no consensus exists regarding a safe level of ethanol consumption for patients with HCV, most experts recommend that patients with HCV abstain from ethanol.

Non-Alcoholic Fatty Liver Disease (NALFLD): This includes a spectrum of liver conditions that range from the typically benign fatty liver to Non-Alcoholic Steatohepatitis (NASH), which can progress to cirrhosis and end-stage liver disease. The disorder NASH is caused by inflammation of the liver in response to intrahepatic fat deposition (in the absence of ongoing ethanol consumption). It can be very difficult to distinguish NASH from alcoholic liver disease based on clinical or histological characteristics. Given the high prevalence of obesity in the US population, NASH has become a very frequent cause of abnormal liver function tests and significant liver disease.

Alpha-1 Antitrypsin (AAT) Deficiency: This rare condition is characterized by deficiency of the AAT enzyme, resulting in overly active proteases in the body and concomitant lung and liver destruction (emphysema and cirrhosis). It has a genetic basis with complex inheritance and variable penetrance, but is most prevalent in Caucasians of Scandinavian descent. In the US and Western Europe, prevalence is estimated between 1 in 2,500 and 1 in 5,000 population. A serum AAT level below 11 micromol/L (80 mg/dL) should prompt specific genetic testing for the most common AAT deficiency alleles.

Hemochromatosis: Defined as an excessive accumulation of iron in the liver, hemochromatosis may be acquired through excessive blood transfusions or erythrocyte disorders, or hereditary when an inherited defect in iron metabolism is present. Type 1 hereditary hemochromatosis is the most common and best-studied variant of this condition and is caused by mutations in the HFE gene. A definitive diagnosis of hemochromatosis requires either liver biopsy with determination of iron index, or a specific battery of genetic testing. Usually hemochromatosis can effectively be ruled out with simple iron studies. A transferrin saturation less than 45% and a serum ferritin less than 200 ng/mL make the presence of hemochromatosis highly unlikely.

Autoimmune Hepatitis: This relatively rare condition results from hepatic inflammation caused by plasma cell infiltration, resulting in fibrosis. Most experts classify autoimmune hepatitis as type 1 or type 2. Type 1 autoimmune hepatitis is by far more common and approximately 50% of persons with type 1 autoimmune hepatitis will have another autoimmune disorder, such as thyroiditis, type 1 diabetes, Grave's disease, or ulcerative colitis. Type 2 autoimmune hepatitis most often affects girls aged 2 to 14 and is rare. Clinical characteristics may include itching, joint pain,
hypergammaglobulinemia, and chronic elevations in aminotransferase levels. An array of autoantibodies, such as anti-nuclear antibodies (ANA), smooth muscle antibodies (SMA), and, in children, anti-liver/kidney microsome type 1 (anti-LKM1), may be useful in the diagnosis. A final diagnosis typically depends on positive autoantibody studies combined with compatible clinical and histologic features. This condition may acutely worsen in the presence of Interferon therapy.
Summary Points

- After confirming chronic hepatitis C infection, the clinician should perform a thorough history, focusing particularly on risk factors for infection, presence of psychiatric disease, significant medical comorbidities, and coinfection with other viruses.
- In the initial evaluation, the clinician should perform a thorough history and physical examination, with a focus on stigmata of chronic liver disease, and manifestations attributable to hepatitis C infection.
- A complete baseline laboratory examination of the newly diagnosed patient includes tests of hepatocellular inflammation, hepatobiliary disease, hepatic function, assays to detect relevant coinfections, and a limited panel of viral-specific measures to assist in staging and counseling regarding treatment.
- In addition to routinely recommended adult immunizations, all persons with chronic hepatitis C infection should be immunized against hepatitis A and B (unless they are immune or have active infection).
- Prior to discussing specific treatment of hepatitis C, the clinician should perform a thorough clinical and laboratory evaluation for other causes and contributors of liver disease.
References

  [CDC and MMWR] -

  [PubMed Abstract] -

  [PubMed Abstract] -

  [PubMed Abstract] -

  [PubMed Abstract] -

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[PubMed Abstract]

[PubMed Abstract]

[PubMed Abstract]

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[PubMed Abstract]

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**Figures**

**Figure 1 CAGE Questionnaire for Detecting Alcoholism**

The CAGE Questionnaire is a simple 4-question screening tool. The acronym CAGE is derived from the question evaluation of Cutting down, Annoyance by criticism, Guilty feeling, and Eye-openers.


<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>C: Have you ever felt you should <strong>Cut</strong> down on your drinking?</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>A: Have people <strong>Annoyed</strong> you by criticizing your drinking?</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>G: Have you ever felt <strong>Guilty</strong> about your drinking?</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>E: Have you ever had a drink first thing in the morning (<strong>Eye opener</strong>)?</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

A total score of 0 or 1 suggests low risk of problem drinking
A total score of 2 or 3 indicates high suspicion for alcoholism
A total score of 4 is virtually diagnostic for alcoholism
Figure 2 AUDIT-C Questionnaire for Detecting Alcoholism

The AUDIT-C is a 3-item screening questionnaire to help identify individuals who have alcohol use disorders (alcohol abuse or dependence). The AUDIT-C is a truncated version of the 10-question AUDIT screen.


<table>
<thead>
<tr>
<th>AUDIT-C Questionnaire for Detecting Alcoholism</th>
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<tbody>
<tr>
<td>1. How often do you have a drink containing alcohol?</td>
</tr>
<tr>
<td>□ a. Never</td>
</tr>
<tr>
<td>□ b. Monthly or less</td>
</tr>
<tr>
<td>□ c. 2-4 times a month</td>
</tr>
<tr>
<td>□ d. 2-3 times a week</td>
</tr>
<tr>
<td>□ e. 4 or more times a week</td>
</tr>
<tr>
<td>2. How many standard drinks containing alcohol do you have on a typical day?</td>
</tr>
<tr>
<td>□ a. 1 or 2</td>
</tr>
<tr>
<td>□ b. 3 or 4</td>
</tr>
<tr>
<td>□ c. 5 or 6</td>
</tr>
<tr>
<td>□ d. 7 to 9</td>
</tr>
<tr>
<td>□ e. 10 or more</td>
</tr>
<tr>
<td>3. How often do you have six or more drinks on one occasion?</td>
</tr>
<tr>
<td>□ a. Never</td>
</tr>
<tr>
<td>□ b. Less than monthly</td>
</tr>
<tr>
<td>□ c. Monthly</td>
</tr>
<tr>
<td>□ d. Weekly</td>
</tr>
<tr>
<td>□ e. Daily or almost daily</td>
</tr>
</tbody>
</table>

The AUDIT-C is scored on a scale of 0-12. Each AUDIT-C question has 5 answer choices. Points allotted are: a = 0 points, b = 1 point, c = 2 points, d = 3 points, e = 4 points. Men, a score of 4 or more is considered positive, optimal for identifying hazardous drinking or active alcohol use disorders. Women, a score of 3 or more is considered positive, optimal for identifying hazardous drinking or active alcohol use disorders.
Body Mass Index (BMI) represents a number calculated based on a person's weight and height and it provides a good rough estimate of a person's body fat. The BMI may overestimate body fat in athletes and underestimate body fat in older persons, or individuals who have lost significant muscle.

Source: National Heart Lung and Blood Institute

**Figure 3 Body Mass Index (BMI) Formula**

Body Mass Index (BMI) represents a number calculated based on a person's weight and height and it provides a good rough estimate of a person's body fat. The BMI may overestimate body fat in athletes and underestimate body fat in older persons, or individuals who have lost significant muscle.

\[
BMI = \frac{\text{weight in pounds} \times 703}{\text{height in inches}^2}
\]

<table>
<thead>
<tr>
<th>BMI</th>
<th>Weight Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Below 18.5</td>
<td>Underweight</td>
</tr>
<tr>
<td>18.5-24.9</td>
<td>Normal</td>
</tr>
<tr>
<td>25.0-29.9</td>
<td>Overweight</td>
</tr>
<tr>
<td>30 and Above</td>
<td>Obese</td>
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</tbody>
</table>
Treatment Nonresponders with hepatitis C therapy include Null Responders (failure to achieve a 2-log reduction in HCV viral load after 12 weeks of therapy) and Partial Responders (achieved a greater than 2-log decrease in HCV viral load at week 12 of therapy, but the HCV RNA level remained detectable at week 24).
Figure 5 Hepatitis C Treatment Relapser

Patients treated for hepatitis C with relapse have an undetectable HCV RNA at the end of treatment, with rebound detectable HCV RNA after completion of therapy.
**Figure 6 Hepatitis A Vaccine Dosages and Schedules for Adults**

Hepatitis A immunization includes an option of two types of hepatitis A vaccines, as well as a combined hepatitis A and B vaccine.

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Dosage</th>
<th>Dosing and Route</th>
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<tbody>
<tr>
<td><strong>Hepatitis A Vaccines</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Havrix</em></td>
<td>1440 EL.U.</td>
<td>2-Dose Schedule: 1 ml given IM at 0 and 6-12 months</td>
</tr>
<tr>
<td><em>Vaqta</em></td>
<td>50 U</td>
<td>2-Dose Schedule: 1 ml given IM at 0 and 6-18 months</td>
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**Combined Hepatitis A and B Vaccines**

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Dosage</th>
<th>Dosing and Route</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Twinrix</em></td>
<td>HAV: 720 EL.U</td>
<td>Standard 3-Dose Schedule: 1 ml given IM at 0, 1, and 6 months or</td>
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<tr>
<td></td>
<td>plus HBsAg: 20 mcg</td>
<td>Accelerated 4-Dose Schedule: 1 ml given IM on days 0, 7, and 21-30, followed by a booster dose at month 12</td>
</tr>
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</table>
**Figure 7 Hepatitis B Vaccine Dosages and Schedules for Adults**

Hepatitis B immunization includes an option of two types of hepatitis B vaccines, as well as a combined hepatitis A and B vaccine.

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Dosage</th>
<th>Dosing and Route</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hepatitis B Vaccines</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Engerix-B</em></td>
<td>20 mcg</td>
<td>3-Dose Schedule: 1 ml given IM at 0, 1, and 6-12 months</td>
</tr>
<tr>
<td><em>Recombivax HB</em></td>
<td>10 mcg</td>
<td>3 doses Schedule: 1 ml given IM at 0, 1, and 6-12 months</td>
</tr>
<tr>
<td><strong>Combined Hepatitis A and B Vaccines</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| *Twinrix*         | HAV: 720 EL.U plus HBsAg: 20 mcg | Standard 3-Dose Schedule: 1 ml given IM at 0, 1, and 6 months  
|                   |        | or  
|                   |        | Accelerated 4-Dose Schedule: 1 ml given IM on days 0, 7, and 21-30, followed by a booster dose at month 12 |
**Figure 8 Potential Secondary Causes of Liver Disease in HCV-Infected Patients**

Abbreviations: AST=aspartate aminotransferase; ALT=alanine aminotransferase; ANA=antinuclear antibody; SMA=smooth muscle antibodies; anti-LKM1=anti-liver/kidney microsome type 1; SPEP=serum protein electrophoresis

<table>
<thead>
<tr>
<th>Secondary Cause of Liver Disease</th>
<th>Potential Diagnostic/Screening Tools</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcoholic Liver Disease</td>
<td>Clinical history, serum AST/ALT ratio, CAGE, AUDIT-C</td>
</tr>
<tr>
<td>Non-Alcoholic Fatty Liver Disease</td>
<td>Liver imaging, serum AST/ALT, exclusion of other causes, liver biopsy</td>
</tr>
<tr>
<td>Alpha-1 Antitrypsin (AAT) Deficiency</td>
<td>Serum AAT levels, genetic testing for AAT deficiency alleles</td>
</tr>
<tr>
<td>Hemochromatosis</td>
<td>Serum Fe studies, hemochromatosis gene testing, liver biopsy with Fe index</td>
</tr>
<tr>
<td>Autoimmune Hepatitis</td>
<td>ANA, SMA, anti-LKM1, SPEP, Liver biopsy</td>
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