Initial Evaluation of Persons with Chronic Hepatitis C

Background

The initial evaluation of persons with hepatitis C virus (HCV) infection may involve a person newly diagnosed with HCV, or an individual previously diagnosed with HCV who is establishing or reestablishing clinical care for the management of their HCV infection. The clinician providing comprehensive HCV-related management can be a primary care clinician with competence in HCV clinical management or an HCV specialist. In the modern HCV treatment era that has safe, effective, and easy-to-use direct-acting antiviral (DAA) agents, the treatment of HCV has expanded into the primary care setting.\(^1\) The capacity of primary care medical providers to treat HCV has also been enhanced by innovative strategies that use HCV treatment experts to support HCV clinical management by primary care medical providers, such as the use of group video conferencing as developed in the Extension for Community Healthcare Outcomes (ECHO) model.\(^2,3\) In addition, the Clinician Consultation Center for Hepatitis C Management provides free clinician-to-clinician advice either by phone (844-437-4636) Monday through Friday 9 a.m. to 8 p.m. EST or by submitting a case online at the Clinician Consultation Center website.
General Approach to Initial Evaluation

First, the clinician should review the hepatitis C test results and confirm the patient has chronic HCV infection (viremic) and not resolved HCV (negative or undetectable HCV viral load).[4] 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 blood-borne viruses (e.g. HIV, hepatitis B virus), stigmata of chronic liver disease, clinical manifestations attributable to hepatitis C infection, prior assessment of liver fibrosis, and a history of prior treatment.[5] Assessment of the stage of liver disease is a complex task and should be addressed in subsequent follow-up visits.
Key Aspects of Medical History

In addition to performing a standard and comprehensive history, 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 potential barriers to treatment.

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 reinfection. In the United States, the major risk factors for HCV acquisition are injection drug use, receipt of a blood transfusion or organ transplant prior to 1992, exposure to an infected sexual partner, occupational needlestick injury, non-sterile tattooing, and mother-to-child transmission.[6] During the past decade there has been a surge in the number of reported new annual acute HCV infections that in large part is attributable to the opioid epidemic and associated injection drug use.[7,8] In addition, there has been recognition of a sexually transmitted hepatitis C epidemic among men who have sex with men (MSM), particularly men with HIV infection.[9,10,11,12] 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.[13,14] Because denial is often intertwined with chronic ethanol use, obtaining an accurate history can be difficult. Several well-validated tools are recommended to screen for alcohol use disorder, including the CAGE Questionnaire, a 4-question screening tool (Figure 1), and the Alcohol Use Disorders Identification Test (AUDIT).[15,16,17] 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).[18] Second, a history of alcohol use may help explain later findings (e.g. increased echogenicity, steatosis, thrombocytopenia) to add important contextual clinical information.

Injection Drug Use History

Injection drug use remains an important risk factor for acquisition of HCV.[19,20,21] For patients with a history of past or present injection-drug use, it is important to assess whether they have active injection drug use, and if they are not actively injecting drugs, whether they 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 coinfections, 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 referrals to harm reduction services and/or treatment and abstinence programs. Ongoing active injection-drug use or use of opioid agonist therapy is not a contraindication to treatment for hepatitis C.[22] The decision to initiate HCV treatment could be impacted by heavy active drug use if it would interfere with the individual's ability to follow-up for scheduled medical appointments. In addition, active injection-drug use in a person successfully treated for hepatitis C places them at risk of becoming reinfected with HCV.[23,24,25]

Prior Staging of Liver Fibrosis

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For persons previously engaged in clinical care for their hepatitis C infection, it is important to determine whether they have had prior evaluation and staging of liver fibrosis. Methods to assess liver fibrosis include serum-based Aspartate aminotransferase-to-Platelet Ratio Index (APRI), FibroTest, liver transient elastography, hepatic ultrasound, and liver biopsy.[26,27] If a liver biopsy has been performed, it is important to document the sample size, fibrosis score, and fibrosis scoring system used in the report.

Complications of Liver Disease

Upon initial evaluation, it is important to determine whether the patient has any history of complications of advanced liver disease. Treatment of HCV in patients with cirrhosis is more complex, and may require referral or consultation with a provider who has expertise in hepatology, particularly if the patient has decompensated cirrhosis. 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 and potentially an evaluation at a liver transplant center.

HCV-Associated Extrahepatic Manifestations

Hepatitis C infection may be associated with a diverse array of extrahepatic manifestations, such as cryoglobulinemia, thyroid disease, arthralgias, neuropathy, nephropathy, glomerulonephritis, lichen planus, insulin resistance, and B-cell lymphomas.[28,29] 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%).[30]

History of Prior Treatment for HCV

For individuals who have previously undergone unsuccessful treatment for HCV the clinician should 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 nonresponse or relapse. Nonresponders are patients who never cleared HCV from their serum during the course of treatment (Figure 3). Relapsers have virologic rebound after achieving an end-of-treatment response, with this usually occurring within the first 12 weeks after treatment completion (Figure 4). As delineated in the American Association for the Study of Liver Diseases and Infectious Diseases Society of America (AASLD-IDSA) HCV Guidance, determining the unsuccessful prior treatment regimen is essential to guide recommendations for future therapy.[31]

Presence of Medical Comorbidities

When evaluating the patient with hepatitis C infection, the clinician should inquire about any secondary causes of liver disease, such as non-alcoholic fatty liver disease (NAFLD), alcoholic hepatitis, alpha-1 antitrypsin deficiency, hemochromatosis, or autoimmune hepatitis.[32,33,34,35,36,37,38] A past or current history of obesity is important to obtain since obesity is strongly associated with the development of NAFLD.[39] The presence of renal impairment may influence treatment regimen as different agents are approved for use in varying stages of chronic kidney disease, and only a select few are safe and approved for use in end-stage renal disease and hemodialysis.

Presence of Significant Coinfections

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Every newly diagnosed patient should be asked about 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.\cite{40,41,42} In persons nonimmune to HAV and HBV, immunization against HAV and HBV should be offered.

**Psychiatric History**

Persons living with chronic HCV infection have a higher incidence of psychiatric illness when compared with the general population.\cite{43,44,45} Inadequately treated psychiatric illness represented a major barrier to successful HCV treatment in the interferon era. In the modern treatment era, psychiatric illness is not a contraindication to treatment, but it may create challenges with regard to linkage to care, HCV treatment adherence, and drug interactions between psychiatric medications and direct-acting antiviral medications.\cite{46,47}
Key Aspects of Physical Examination

Physical Examination of a Patient with HCV Infection

During the initial evaluation visit, the clinician should ideally perform a complete physical examination, including obtaining the patient's height and weight to determine the body mass index (BMI). In addition, there are several liver-related physical findings that should be specifically sought that may identify the presence of indicators of advanced liver disease. The calculation of an individual's BMI is based on their weight (pounds) and height (inches) (BMI Calculator) (Figure 5). The National Heart, Lung, and Blood Institute has BMI Tables for interpreting the calculated BMI result.

Physical Examination Findings in Patients with Cirrhosis

The following is a description of some of the key physical examination findings that should indicate the presence of cirrhosis.[48,49,50,51]

- **Ascites** (Figure 6): Ascites, which is defined as an abnormal accumulation of fluid in the abdominal cavity, is the most common complication of cirrhosis, with approximately 50% of patients with compensated cirrhosis developing ascites over a 10-year period. The presence of bulging flanks suggests the presence of ascites.[52] In order for the flank dullness to be appreciated on physical exam, at least 1500 mL of fluid needs to be present. The shifting dullness test improves the diagnostic sensitivity of physical examination for detecting the presence of ascites.[52]

- **Distended Abdominal Veins and Caput Medusae** (Figure 7): 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 as caput medusae.[53,54] On general inspection, the cirrhosis-related abdominal vein swelling can appear similar to findings with obstructions of the inferior vena cava.

- **Gynecomastia** (Figure 8): The presence of true gynecomastia 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.[55] Cirrhosis-related gynecomastia results from impaired hepatic degradation of estrogens, a problem enhanced in patients with excess alcohol consumption (because of the phytoestrogens in alcohol). The finding of gynecomastia is not specific to cirrhosis.[55,56]

- **Jaundice** (Figure 9): The term jaundice refers to a yellow discoloration of the skin or sclera that results from excess deposition of biliary pigments. The sclera and mucous membranes under the tongue are the most sensitive sites to detect jaundice.[57] Jaundice is usually detected only when the serum bilirubin level exceeds 2.5 mg/dL. In one study, 58% of clinicians were able to detect scleral icterus when the serum bilirubin was 2.5 mg/dL and 68% when the serum bilirubin was 3.1 mg/dL.[57] The finding of jaundice is often an indicator of advanced liver disease, and in persons with chronic liver disease it strongly suggests decompensated cirrhosis. Jaundice can result from non-hepatic causes, such as hemolytic anemia.

- **Palmar Erythema** (Figure 10): The finding of palmary erythema is suggested by the presence of intense erythema in the thenar and hypothenar eminence (base of the thumb and fifth finger) of the palm, with the central region of the palm spared.[58] Approximately 25% of persons with cirrhosis have palmar erythema. This finding is not specific to cirrhosis and can be seen in pregnant women, thyrotoxicosis, and rheumatoid arthritis.[50]

- **Spider Nevi (Spider Angiomata)** (Figure 11): 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.[59] With direct compression on the central region of the lesion, the lesion will temporarily blanch, but with release of pressure the lesion fills 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. In patients with cirrhosis, elevated levels of vascular endothelial growth factor (VEGF), basic fibroblastic growth factor (bFGF), and substance P are thought to play a role in the development of spider angioma.[60]

- **Terry’s Nails** (Figure 12): The initial finding of Terry’s nails consists of a white-silver discoloration of the proximal nail bed, typically with a pink band on the distal portion of the nail bed; as this process progresses, the white discoloration can involve about 80% of the nail bed, with only a 0.5 to 3.0 mm pink band remaining on the distal nail plate.[61,62] This finding can be distinguished from onychomycosis, since Terry’s nails involves the nail bed and has a pink-brown band, whereas onychomycosis involves the nail itself, without any pink distal band.

### Accuracy of Physical Examination 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 a patient has cirrhosis: distended abdominal veins, encephalopathy, ascites, and spider nevi (all with a likelihood ratio [LR] greater than 4). Although Terry’s 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, in decreasing order of positive likelihood ratio (LR) for the presence of cirrhosis:

- Terry's 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 Initial Laboratory Studies**

**Initial Laboratory Evaluation**

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.[5] The major goals of the initial laboratory evaluation are two-fold: (1) identify any abnormalities directly related to the HCV-related liver injury, such as thrombocytopenia, liver dysfunction, or inflammation, and (2) evaluate for any common extrahepatic manifestations of chronic HCV infection, such as thyroid disease, cardiovascular disease, or renal disease.[5,28] This same approach for ordering initial laboratory studies should be used during the initial evaluation for patients who are reestablishing medical care for their hepatitis C infection.

- **General Laboratory Evaluation**: Complete blood count (CBC), platelet count, serum creatinine, and thyroid function tests (TSH).
- **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 pretreatment 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 and does not determine who should receive treatment.
- **HCV Genotype**: Hepatitis C virus exists as one of six main distinct genotypes, each with slightly different epidemiologic and clinical characteristics. In the United States, HCV genotype 1 is most common, accounting for 74% of cases. Determining the HCV genotype is recommended, because some treatment regimens and duration differ based on the HCV genotype. With the availability of several pangenotypic DAA regimens, obtaining the HCV genotype has become less important.
- **IL-28B Testing**: The single nucleotide polymorphism (SNP) at the IL-28B locus codes for interferon lambda and strongly correlates with interferon-based HCV treatment responses. This polymorphism also explains much of the observed racial and ethnic variation in response to hepatitis C treatment with interferon-based therapy. Patients who are C/C homozygous typically have a greater chance of spontaneous clearance of HCV and the best treatment response to interferon-based therapies. In the current era of DAA therapy, performing IL-28B testing is not recommended as it has been shown to be less predictive of treatment outcome.
**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.[40] The hepatitis A immunization can be accomplished via a two-dose, single hepatitis A antigen vaccine or as a 3-dose Hepatitis A/B combination vaccine (Figure 13).[63] Checking post-vaccination hepatitis A titers is not recommended, primarily because of the very high response to hepatitis A vaccine.[63]

**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. Traditionally, the hepatitis B vaccine series consists of a three-dose series using recombinant HBV vaccine, but recently a 2-dose hepatitis B vaccine series that can be completed in 1 month has been FDA-approved and this new hepatitis B vaccine utilizes the CpG 1018 adjuvant; there is also a 3-dose series hepatitis A/B combination vaccine available (Figure 14).[64,65,66]

**Pneumococcal Immunization**

The Advisory Committee on Immunization Practices (ACIP) recommends that persons aged 19 through 64 with chronic liver disease receive one dose of the 23-valent polysaccharide pneumococcal vaccine (PPSV23).[67,68] At age 65, all adults, including those with liver disease, should receive one dose of pneumococcal conjugate vaccine (PCV13) and a dose of PPSV23, with the dose of PPSV23 given at least 1-year after the PCV13 and at least 5 years after any prior dose of PPSV23 they may have received.[67] Currently, there are no recommendations to give PCV13 specifically for chronic liver disease.[67]

**Routine Adult Vaccines**

Entry into care represents an opportunity to administer 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 of Liver Disease

Overview of Screening for Other Causes of Liver Disease

In the course of a complete workup 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. Other causes of liver disease may coexist with HCV infection, including both hereditary and acquired conditions (Figure 15). Identifying additional causes of liver disease in persons with chronic HCV is important since the combination of diseases may result in accelerated fibrosis progression or ongoing fibrosis progression even after HCV eradication. 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 some of the most important nonviral causes of hepatic inflammation.

Alcoholic Liver Disease

Chronic excessive alcohol consumption is the most common cause of liver disease in the Western world and determining alcohol intake is important in patients with hepatitis C infection.[70,71] On a practical basis, differentiating liver injury caused by alcohol use from that due to chronic HCV infection can be difficult, but the finding of an AST/ALT ratio of greater than 2.0 suggests alcohol-related injury, although this pattern may also be seen in advanced cirrhosis of any cause.[72,73] In addition, screening for alcohol intake as part of the medical history, as outlined above, may provide useful information on whether alcohol is a likely contributor to liver disease. Excessive alcohol use can cause acute alcoholic hepatitis, fatty liver (steatosis), and eventually cirrhosis.[70,73,74] In addition, alcohol use clearly accelerates HCV-associated fibrosis and hastens the onset of cirrhosis.[75,76] Given that no consensus exists regarding a safe level of alcohol consumption for persons with chronic HCV infection, most experts recommend they abstain from alcohol.[77]

Nonalcoholic Fatty Liver Disease (NAFLD)

Globally, an epidemic in chronic liver disease caused by nonalcoholic fatty liver disease (NAFLD) has emerged due to changes in lifestyle and increasing prevalence of obesity.[78] In the United States, the prevalence of obesity is high and the NAFLD prevalence in adults is estimated at approximately 24%.[79] The AASLD defines NAFLD as (1) evidence of hepatic steatosis documented either by imaging or histologic findings on liver biopsy, and (2) lack of any secondary cause of hepatic fat accumulation, such as significant alcohol consumption, long-term use of a steatogenic medication, or monogenic hereditary disorders.[80] Common conditions that have an established association with NAFLD include obesity, dyslipidemia, type 2 diabetes mellitus, metabolic syndrome, and polycystic ovary syndrome.[80] The AASLD classifies NAFLD into two subcategories—nonalcoholic fatty liver (NAFL) and nonalcoholic steatohepatitis (NASH) based on histologic findings: (1) NAFL is defined as 5% or more hepatic steatosis without evidence of hepatocellular injury and (2) NASH is defined as 5% or more hepatic steatosis with evidence of hepatocellular inflammation and injury.[35] The development of NASH can result in progression to cirrhosis, liver failure, and hepatocellular cancer.[78,81] The diagnosis of NALFD requires documented absence of ongoing or recent substantial alcohol ingestion.[35] Two radiographic tests—magnetic resonance imaging by spectroscopy or magnetic resonance imaging with proton hepatic assessments—appear promising as noninvasive methods to estimate the degree of hepatic steatosis, but liver biopsy remains the gold standard for determining the presence and severity of NAFLD.[35]

Alpha-1 Antitrypsin Deficiency

This rare condition is characterized by deficiency of the alpha-1 antitrypsin enzyme, resulting in overly active proteases in the body and concomitant lung and liver destruction (emphysema and
cirrhosis).\[82,83\] It has a genetic basis with complex inheritance and variable penetrance, but is most prevalent in Caucasians of Scandinavian descent. In the United States and Western Europe, the prevalence of alpha-1 antitrypsin deficiency is estimated between 1 in 2,000 and 1 in 5,000 population.\[83\] A serum alpha-1 antitrypsin level below 11 μmol/L (80 mg/dL) should prompt specific genetic testing for the most common alpha-1 antitrypsin deficiency alleles.\[38\]

**Hemochromatosis**

Hemochromatosis is defined as an excessive accumulation of iron in the liver; hemochromatosis may result from excessive blood transfusions, erythrocyte disorders, or as a hereditary condition that involves a defect in iron metabolism.\[69\] With hereditary hemochromatosis, the total amount of body iron accumulates over time, which is associated with increased hepatic iron that can eventually cause tissue injury and cirrhosis.\[84\] Type 1 hereditary hemochromatosis is the most common and best-studied hereditary hemochromatosis variant and is caused by mutations in the human factors engineering (HFE) gene.\[85\] Initial diagnostic laboratory studies that suggest a diagnosis of hemochromatosis include elevated serum iron, elevated serum ferritin concentration, and elevated transferrin saturation.\[84,85\] A definitive diagnosis of hemochromatosis requires either liver biopsy with determination of iron index, or a specific battery of genetic testing. For screening purposes, most expert guidelines, including those from the American Association for the Study of Liver Diseases (AASLD), recommend using the following cutoffs when screening for iron overload: transferrin saturation greater than 45% and a serum ferritin greater than 200 ng/mL (for men) and greater than 150 ng/mL (for women).\[86,87,88\]

**Autoimmune Hepatitis**

This relatively rare condition results from both genetic and host factors. The disorder is believed to result from the host losing tolerance to its own liver antigens, which leads to an immune response that includes activated immune cells, autoantibodies, interferons, and proinflammatory cytokines, which together cause hepatic inflammation.\[89,90\] Most experts classify autoimmune hepatitis as type 1 or type 2.\[34,90\] Autoimmune hepatitis-1 is more common than autoimmune hepatitis-2 and can affect children or adults, although it predominantly occurs in adults. Approximately 20% of persons with autoimmune hepatitis-1 will have an extrahepatic autoimmune disorder, such as autoimmune thyroid disease, arthritis, or inflammatory bowel disease.\[90\] Autoimmune hepatitis-2 most often affects children and extrahepatic autoimmune complications are common, including autoimmune thyroid disease, insulin-dependent diabetes mellitus, Addison's disease, and arthritis.\[90\] Clinical and laboratory characteristics with autoimmune hepatitis include itching, joint pain, hypergammaglobulinemia, and chronic elevations in aminotransferase levels. The diagnosis typically depends on positive autoantibody studies combined with compatible clinical and histologic features.\[91,92\] Autoantibodies commonly found in persons with autoimmune hepatitis include smooth muscle antibodies (SMA), antinuclear antibodies (ANA), antimitochondrial antibodies (AMA), liver-kidney microsomal antibodies (LKM), and soluble liver/liver-pancreas antibodies (SLA/LP).\[93\] In 2008, the International Autoimmune Hepatitis Group published revised simplified criteria for the diagnosis of autoimmune hepatitis.\[93\]
**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.
Citations


22. AASLD-IDSA. Recommendations for testing, management, and treating hepatitis C. When and in whom to initiate HCV therapy. [AASLD-IDSA Hepatitis C Guidance] -


31. AASLD-IDSA. Recommendations for testing, management, and treating hepatitis C. Retreatment of persons in whom prior therapy failed. [AASLD-IDSA Hepatitis C Guidance]


67. Advisory Committee on Immunization Practices. Recommended Immunization Schedule for Adults Aged 19 Years or Older by Medical Conditions and Other Indications, United States, 2018. [ACIP]


77. AASLD-IDSA. Recommendations for testing, management, and treating hepatitis C. HCV testing and linkage to care. [AASLD-IDSA Hepatitis C Guidance]


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  [PubMed Abstract] -

  [PubMed Abstract] -

  [PubMed Abstract] -

  [PubMed Abstract] -
# 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>Question</th>
<th>Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. How often do you have a drink containing alcohol?</td>
<td>a. Never</td>
</tr>
<tr>
<td></td>
<td>b. Monthly or less</td>
</tr>
<tr>
<td></td>
<td>c. 2-4 times a month</td>
</tr>
<tr>
<td></td>
<td>d. 2-3 times a week</td>
</tr>
<tr>
<td></td>
<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>
<td>a. 1 or 2</td>
</tr>
<tr>
<td></td>
<td>b. 3 or 4</td>
</tr>
<tr>
<td></td>
<td>c. 5 or 6</td>
</tr>
<tr>
<td></td>
<td>d. 7 to 9</td>
</tr>
<tr>
<td></td>
<td>e. 10 or more</td>
</tr>
<tr>
<td>3. How often do you have six or more drinks on one occasion?</td>
<td>a. Never</td>
</tr>
<tr>
<td></td>
<td>b. Less than monthly</td>
</tr>
<tr>
<td></td>
<td>c. Monthly</td>
</tr>
<tr>
<td></td>
<td>d. Weekly</td>
</tr>
<tr>
<td></td>
<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.
Figure 3 Hepatitis C Treatment Nonresponse

Treatment Nonresponders with hepatitis C therapy are those who have failed to achieve an undetectable HCV RNA level after a course of therapy (in this example showing response with 12 weeks of therapy).
Figure 4 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 5 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.

Source: National Heart Lung and Blood Institute

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

<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>
</tr>
</tbody>
</table>
**Figure 6 Ascites**

The presence of bulging flanks suggests a possible diagnosis of ascites; this should be confirmed with a shifting dullness test.

Illustration: Illustration by Jared Travnicek, Cognition Studio
Figure 7 Caput Medusa

Caput medusa results from portal hypertension and is manifested as distended abdominal veins radiating around the umbilicus.

Illustration: Illustration by Jared Travnicek, Cognition Studio
**Figure 8 Gynecomastia**

In men with cirrhosis, benign enlargement of the breasts may occur and manifest as gynecomastia.

Illustration: Illustration by Jared Travnicek, Cognition Studio
Figure 9 Jaundice

This illustration shows yellow discoloration of the sclera that results from excess deposition of biliary pigments.

Illustration: Illustration by Jared Travnicek, Cognition Studio
Figure 10 Palmar Erythema

With palmar erythema, the redness is most prominent in the thenar and hypothenar eminence, with sparing of the central region of the palm.

Illustration: Illustration by Jared Travnicek, Cognition Studio
**Figure 11 Spider Angiomata**

Spider angiomata are enlarged cutaneous blood vessels that resemble the appearance of spider. Compression of the central aspect of the lesions causes the entire lesion to blanch; with release of compression the blood quickly refills and the red color reappears.

Illustration: Illustration by Jared Travnicek, Cognition Studio
**Figure 12 Terry's Nails**

Note the white-silver discoloration of the proximal nail bed and the pink band on the distal portion of the nail bed.

Illustration: Illustration by Jared Travnicek, Cognition Studio
**Figure 13 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>
</tr>
</thead>
<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>
</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 14 Hepatitis B Vaccine Dosages and Schedules for Adults**

Hepatitis B immunization includes an option of three 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-Dose Schedule: 1 mL given IM at 0, 1, and 6-12 months</td>
</tr>
<tr>
<td><em>Heplisav</em></td>
<td>20 mcg</td>
<td>2-Dose Schedule: 1 mL given IM at 0 and 1 month</td>
</tr>
<tr>
<td><strong>Combined Hepatitis A and B Vaccines</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Twinrix</em></td>
<td>HAV: 720 EL.U plus HBsAg: 20 mcg</td>
<td>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</td>
</tr>
</tbody>
</table>
**Figure 15 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>
</tr>
</tbody>
</table>