Boston Healthcare for the Homeless Program Primary Care Guideline for the Care of Patients with Chronic Hepatitis C

Rationale for Hepatitis C (HCV) Guideline:

HCV is a highly prevalent infection in the BHCHP patient population. [1]

HCV contributes to significant morbidity and mortality.[2,3]

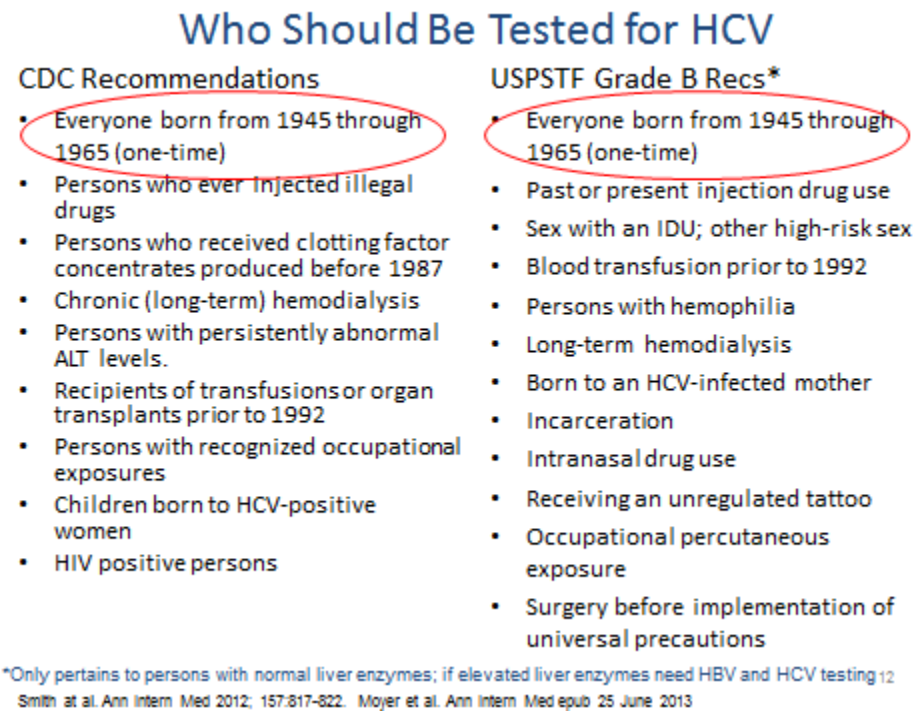
Effective therapy is available for treatment of HCV and a cure is achievable for a large proportion of patients who are treated.[3]

Achieving a cure for HCV (sustained virologic response, SVR) reduces all- cause mortality.[4] SVR also reduces risk of liver cancer, progression of liver disease, need for liver transplant, and risk of liver-related death.[5]

The presence of chronic HCV infection impacts general medical care decisions.[3]

Hepatitis C (HCV) Screening:

Revised 2012 HCV screening recommendations from the Centers for Disease Control (CDC) and the USPSTF identify the following risk groups for routine screening:



Considering the known high prevalence of hepatitis C at BHCHP, an enhanced level of screening is recommended.

- **All patients at BHCHP should receive one-time screening for hepatitis C by hepatitis C antibody testing regardless of risk factors.**
- **Ongoing screening should be conducted on an annual basis for patients who are at high risk to acquire HCV.** These risk factors include: injection drug use, sex with injection drug users, anal receptive sex,[8] long-term hemodialysis, occupational exposures, incarceration, intranasal drug use, unregulated tattooing, and HIV infection.
- **Patients with a previous exposure to HCV (HCV antibody positivity) but an undetectable HCV viral load due to spontaneous viral clearance or treatment, should undergo annual screening with HCV viral load if they have ongoing risk factors** as HCV antibody-positivity is not protective against reinfection.[3]

Hepatitis C Diagnosis:

Hepatitis C antibody positivity confirms *exposure* to the HCV virus.

HCV viral load testing is required to confirm chronic infection. The presence of an HCV VL confirms chronic HCV infection. Note, however, that the viral load value does not predict degree of liver fibrosis or risk for progression to advanced liver disease. There is no indication to serially monitor viral loads in persons not undergoing HCV treatment.

HCV antibody with undetectable HCV VL can have several interpretations:

- resolved HCV infection
- chronic infection with low-level viremia and transient undetectable HCV RNA
- acute infection with transient clearance of HCV RNA
- a false positive HCV antibody test

These patients should have a repeat quantitative HCV RNA test performed in 4-6 months. "If acute HCV is suspected (e.g. recent risk behaviors for infection), the repeat testing should be performed in 8-12 weeks. **If the initial and repeat HCV RNA tests are negative, the patient most likely has resolved HCV infection**."[3]

Special cases: Indications for evaluating HCV VL in HCV antibody negative patients

- suspected acute infection
- unexplained persistently elevated ALT levels
- advanced immunosuppression due to HIV (CD4 <100/mm^3)

- those receiving hemodialysis.

"If HCV RNA testing is negative in this setting, the patient is considered to have no evidence of past or current HCV infection."[3]

Acute Hepatitis C

Acute HCV infection is defined as the first 6 months after acquisition of HCV infection. It is not commonly identified during the acute phase, but may be identified by acute onset of gastrointestinal symptoms (including nausea, vomiting, and jaundice), acutely elevated liver function tests or in the setting of known recent exposure.

Due to complexity of lab screening, as well as potential for successful treatment using alternative or atypical regimens, referral to liver specialty should be facilitated as soon as possible if acute HCV infection is suspected.[9,10]

Primary Care Management of Chronic Hepatitis C

Routine Health Maintenance and Patient Education

Screening labs and vaccinations:

- Hepatitis A and B serologies should be checked to determine presence of coinfection or need for immunization. It is important to ensure hepatitis A and B immunity in patients with hepatitis C due to increased morbidity and mortality associated with coinfection.
- HIV screening should be conducted at least once in patients with HCV. Annual screening recommended for ongoing risk factors.
- Vaccinate for Flu and Pneumococcal Pneumonia

Screen for risk for transmission to others:

- Support harm reduction strategies in active IV drug users to prevent spread of HCV infection. Counsel on importance of using clean needles AND works (cookers, cottons, waters). Counsel and refer for drug treatment as appropriate
    - **Screen for risk for opiate overdose and prescribe nasal narcan as appropriate**
- Counsel patients to avoid sharing toothbrushes and dental or shaving equipment and cover any cut or sore in order to prevent contact of their blood with others
- Safe sexual practices should be recommended in patients with multiple partners and those who engage in anal sex as there is increased risk of transmission through blood contact with this high risk activity[3]

Patient liver health screening and education:

- Screen for alcohol use and counsel to reduce or cease alcohol consumption- offer treatment or refer as appropriate
- Avoid taking iron supplements unless documented deficiency[3]
- There is no clear consensus among expert groups around safe dosing for acetaminophen in HCV. Some indicate that up to 4 grams/day is safe in all cases except acute liver injury while others support 2 grams/day maximum dosing in patients with cirrhosis or chronic alcohol intake.[11]
- NSAIDs should be avoided in patients with cirrhosis due to increased risk for variceal hemorrhage, impaired renal function and risk for development of diuretic-resistant ascites [11]

Lab evaluation:

Overview of frequency:

At baseline: In addition to health screening labs above, HCV VL, HCV genotype*, CBC, PT/INR, basic metabolic panel (BMP), liver function tests (LFTs), **Fib-4 index** (see below for justification of Fib-4).

It is reasonable to obtain a baseline abdominal ultrasound to evaluate for hepatocellular cancer (HCC) at time of diagnosis. There is no role for serial abdominal ultrasound monitoring after this point unless the patient has a diagnosis of cirrhosis.[12]

Q6 month monitoring **for cirrhotic patients only**: CBC, PT/INR, BMP, LFTs and abdominal ultrasound

Q12 months for all patients: CBC, PT/INR, BMP, LFTs**, Fib-4 index**

Only check for cyroglobulins in HCV patients presenting with symptoms such as palpable purpura, arthralgias, renal disease, or peripheral neuropathy[3]

*HCV genotype should be checked once. There are 6 major HCV genotypes. The genotype should be obtained because it provides valuable prognostic information with respect to treatment response and helps determine ribavirin dosing if applicable.[3]

Screening for Other Causes of Liver Disease

"In some patients, other causes of liver disease may be suspected. Screening tests and suspected diseases may include the following: hepatitis B surface antigen (HBsAg); iron, ferritin, and total iron binding capacity(hemochromatosis); ceruloplasmin (Wilson's disease); anti-mitochondrial antibodies (primary biliary cirrhosis); anti-nuclear and anti-smooth muscle antibody (autoimmune hepatitis); and alpha-1 anti-trypsin level (alpha-1 anti-trypsin deficiency). Evaluation for hepatic steatosis requires liver biopsy."[3]

Fibrosis Assessment and diagnosing cirrhosis

The goal of fibrosis assessment is

- To identify the degree of liver scarring in an individual patient
- To diagnose cirrhosis, which confers higher risk for liver-related complications including liver cancer, and indicates need for increased screening and monitoring

- To help guide treatment decisions including timing, duration and likelihood of response

There are multiple modalities to assess hepatic fibrosis. Liver biopsy is the gold standard. Additional evaluation options include noninvasive tests like the APRI score, Fib-4 index, Fibrotest/Fibrosure/Hepascore, and Fibroscan (transient elastography). **None of these evaluations is 100% sensitive or specific.** See the table below for comparison of performance across the non-invasive fibrosis assessments.

Selected Noninvasive Systems to Assess Liver Fibrosis in Chronic Hepatitis C

Marker	Description	Performance
AST to platelet ratio index (APRI)	(AST level/ULN x 100)/ platelet count	Threshold of 0.7 has a sensitivity of 77% and specificity of 72% for significant fibrosis (Metavir stage 3 or 4)[13]
FIB-4 index	**(Age (yrs) x AST (IU/mL))/(platelets (x 1000) x ALT (IU/mL)$^{1/2}$)**	**Index of > 3.25 has PPV of 82% with a specificity of 98% for significant fibrosis (Metavir stage 3 or 4)[14]**
FibroTest	Calculation including age, haptoglobin, alpha-2-macroglobulin, apolipoprotein A1, GGT, and total bilirubin	Sensitivity of 75% and specificity of 85% to detect Metavir stage 2 or greater[15]
FibroScan	Ultrasound device that uses transient elastography to assesses liver shear wave velocity (meters/second) that is converted to equivalent liver stiffness (kilopascals) at 50 Hz, which correlates with hepatic fibrosis stage	Threshold for diagnosis of cirrhosis 12.5 KPa with sensitivity of 87% and specificity of 91%[16,17]

[18]

In the interest of applying an accurate, easily administered, cost-effective measure that enables BHCHP to identify the highest risk patients for morbidity and mortality to the large population of patients with HCV at BHCHP, the Fib-4 index is chosen as the preferred fibrosis staging instrument.

Fib-4 index =(age (yrs) x AST (Iu/mL)/(platelets (x1000) x ALT (IU/mL)$^{1/2}$)

The Fib-4 index performs well, is very low cost (free calculation based on routine labs obtained already), allows for population management and triage of more advance fibrosis and cirrhosis cases, and has been validated in multiple populations including HIV/HCV coinfection[19], as well as over time.[20] By comparison, other noninvasive tests are more costly and/or less accurate. While individual clinician's may wish to utilize these other tests, the application of the Fib-4 index as a standardized fibrosis assessment tool is preferred. Of note, biopsy will continue to be available, but is invasive, with risk of serious side effects, is subject to sampling error, and can be difficult to coordinate in our patient population.[10,21]

Fib-4 index results are reported as such:

- <1.45= highly suggestive of minimal fibrosis (F0-F1)

- >3.25=highly suggestive of advanced fibrosis (F3-F4)
- 1.46-3.24= indeterminate level of fibrosis

The results predict a level of fibrosis based on the Metavir scale.

Metavir scale of fibrosis

• F0 = no fibrosis.
• F1 = portal fibrosis w/o septa.
• F2 = few septa.
• F3 = numerous septa w/o cirrhosis
• F4 = cirrhosis.

The **Fib-4 index is most clinically useful in identifying minimal (F0-F1) and advanced (F3-F4) disease** but does not perform well at discriminating between intermediate levels of fibrosis. As such, if a patient scores in the intermediate range on the Fib-4 but has other suspicious signs of cirrhosis he/she should be evaluated further with another fibrosis assessment modality.

The Fib-4 index tool should be calculated annually and will be available through the EMR.

Patients who are identified to have advanced disease by a Fib-4 index score >3.25 should be considered likely cirrhotic

Cirrhosis management:

Most cirrhotics are ***compensated***, meaning that their liver function tests, platelet levels and INR may be normal or close to normal. It is extremely important to identify cirrhosis as early as possible, through the Fib-4 index evaluation or other means, to enable appropriate monitoring and prevention of decompensation.

About 12% of cirrhotic patients are ***decompensated,*** meaning they have developed ascites, bleeding esophageal varices, hepatic encephalopathy or jaundice.[22]

Any patient with likely cirrhosis (Fib-4 >3.25) should receive:

- **Increased frequency of lab monitoring to q6mo** (CBC/diff, PT/INR, CMP)
- **HCC screening with abdominal ultrasounds q6 months**[12]
    - Of note, AFP screening, though previously recommended in conjunction with abdominal ultrasound screening for HCC surveillance, is no longer recommended by AASLD due to its inadequate sensitivity and specificity.[3,12]
- **Esophageal varices screening with endoscopy**[23] (frequency of follow up EGD based on results)
- **Consideration for HCV treatment**

- **More frequent clinical evaluation q6 months** for signs and symptoms of decompensation, including evaluating for hepatic encephalopathy, ascites, lower extremity edema, signs of increased bleeding or bruising, spider angiomata, jaundice, palmar erythema, gynecomastia, and testicular atrophy.

While the primary care provider may feel comfortable managing cirrhosis in his/her practice, it is recommended to consider referring cirrhotic patients to a hepatologist for consultation and management of possible decompensation and possible future need for transplant.

HCV Treatment

Effective therapy is available for treatment of HCV and a cure is achievable for a large proportion of patients who are treated.[3]

Achieving SVR (sustained virologic response or cure) is associated with decrease in mortality from liver cancer and liver disease as well as all-cause mortality.[4]

Increasingly effective and well tolerated HCV treatment regimens are available and will be offered by BHCHP providers with expertise in HCV treatment. Providing the option of HCV treatment at BHCHP will enable BHCHP patients greater access to treatment as well as improved coordination and support between primary, behavioral, addiction and HCV specialty care. Providers may still refer to hepatology for treatment as they prefer.

Patients with advanced fibrosis are greatest priority for treatment, but all patients with HCV should be counseled about the availability of treatment and evaluated for treatment annually.

Active drug use is not a contraindication for treatment.[24] Patients who are high risk to transmit HCV to others should be considered high priority for treatment.

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