

REVIEW ARTICLE

Hepatitis C – Screening, Diagnosis, Management & Treatment

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KEYWORDS:

Disease Prevention
and Wellness

Hepatitis C

Infectious Disease

Jaundice

Transaminitis

Abstract: Hepatitis C virus (HCV) infection is a major cause of chronic liver disease, hepatocellular carcinoma and cirrhosis with at least 185 million people infected worldwide, causing 399,000 deaths annually. HCV is transmitted through blood or body fluids. Transmission most commonly occurs through sharing of injection drug, occupational exposure through needlestick injuries in healthcare settings, and birth to an HCV infected mother. There are seven known genotypes of HCV, 1a, 1b, 2, 3, 4, 5, and 6, with the most common genotypes in the U.S. being 1a, 1b, 2, and 3, which comprise approximately 97% of all U.S. HCV infections. Risks for disease progression include baseline liver histology, age, ethnicity, gender, alcohol use, comorbidities and immune response. There are multiple screening recommendations currently in place, some of which are based on risk factors, with others based on legislation. The screening test of choice is the anti-Hepatitis C virus antibody, with a confirmatory HCV RNA PCR with genotyping. Once the diagnosis is made, assessing the level of fibrosis and/or cirrhosis is an important step in determining the pathway to treatment. There are multiple new options for treatment with improved efficacy and less side effects. Patient being treated for HCV should be monitored and assessed for compliance with therapy and adverse effects, including new or worsening psychiatric illness and screened for alcohol and substance abuse. Several studies have shown the long-term outcomes with the above treatments reducing morbidity and mortality. A summary of key clinical recommendations can be found in *Table 1*.

INTRODUCTION AND BACKGROUND

Hepatitis C virus (HCV) infection is a major cause of chronic liver disease, hepatocellular carcinoma and cirrhosis worldwide.¹ The World Health Organization reports that there are at least 185 million persons worldwide with the infection, causing 399,000 deaths annually.¹ In 2014, the Center for Disease Control reported 20,000 deaths in which HCV infection was a factor in the US.² Globally, 71 million people have chronic HCV infection, while in the United States, an estimated 2.7-3.9 million individuals are chronically infected with HCV.² In 2015, there were an estimated 34,000 new HCV infections in the US, a 2.9-fold increase from 2010.²

The burden of HCV infection in the United States is expected to increase as the large number of individuals infected in the 1960's and 1970's are tested due to new guidelines and legislation.³ The CDC also predicts an increased burden in younger populations with the current opioid epidemic.² In 2013, the total cost of HCV infection in the United States was estimated at \$6.5 billion.⁴ Chronic HCV infection leads to significantly more lost days of work, decreased productivity, and increased health care costs.⁵ Chronic HCV infection is also the leading indication for liver transplant in the US.²

PATHOPHYSIOLOGY

There are seven known genotypes of HCV, 1a, 1b, 2, 3, 4, 5, and 6. The most common genotypes in the United States, comprising approximately 97% of all US HCV infections, are 1a, 1b, 2, and 3.6 The mechanism of hepatocyte damage induced by HCV infection is not completely understood but may involve direct cell injury and a local immune-mediated mechanism that causes a chronic inflammatory state.^{7,8} Acute HCV infection progresses to chronic infection (detectable virus after 6 months) in 75% to 85% of cases and clears spontaneously in 15% to 25% of patients.² Of those originally infected, 60-70% will develop chronic liver disease (stable chronic infection and/or development of hepatic fibrosis), 5-20% will develop cirrhosis over a period of 20-30 years, 1-5% will die of a HCV infection-related complication and 1-3% will develop hepatocellular carcinoma.²

RISKS FOR DISEASE PROGRESSION

Risks for disease progression include abnormal baseline liver histology, age, ethnicity, gender, alcohol use, comorbidities and cellular immune response. Patients with HIV, Hepatitis B, diabetes¹³, obesity¹⁴ and Vitamin D deficiency (<10ng/ml)¹⁵ are associated with faster progression to fibrosis. Male gender and HCV infection after age 40-55 are also associated with faster progression to fibrosis.^{10, 11} Patients with less inflammation and less hepatic fat on histology or by non-invasive evaluation are at lower risk for progression to cirrhosis.⁹ Progression in African American patients appears to be slower.¹²

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TABLE 1:

Summary of key clinical recommendations

RECOMMENDATION	EVIDENCE RATING	REFERENCES
Patients at high risk for acquisition of HCV should be screened periodically, and those born between 1945-1965 should be screened once.	B	16, 18
Initial screening should be performed with qualitative HCV antibody test	C	1, 18
Confirmation of positive screen should be performed with quantitative HCV RNA viral load by PCR with genotyping prior to starting treatment	A	1, 16
All patients with chronic HCV infection being evaluated for treatment should be assessed for degree of fibrosis and cirrhosis	C	1, 16
All patients with chronic HCV infection should be considered for treatment based on genotype, degree of fibrosis, prior treatment, comorbidities and potential adverse effects.	C	1, 16
All patients undergoing treatment should be screened for alcohol use, illicit drug use and new/worsening psychiatric disorders at every visit	C	1, 16
Immunization for Hepatitis A and B is recommended for susceptible patients with HCV infection	C	16

MODES OF TRANSMISSION & RISK FACTORS FOR TRANSMISSION

HCV is a blood borne virus and predominantly transmitted through blood or body fluids.^{1,16} It is most commonly transmitted through sharing of injection equipment associated with injection drug abuse, needlestick injuries in the healthcare setting, and birth to an HCV infected mother.² In the US, transmission via blood, blood products or organ transplantation was once the most common mode of transmission, however, with the onset of blood screening in 1992, this is now exceptionally rare.² The CDC reports that the chances of HCV infection through blood products is now less than 1 per 2 million units transfused. Other less efficient modes of transmission include sex with an HCV infected partner and sharing of personal effects (razors, toothbrushes, etc.). However, sexual practices where there is a chance of blood-to-blood contact increase the possibility of transmission.¹⁷

Intravenous drug use is the most important risk factor for HCV infection, accounting for approximately 60% of acute infections in the United States.⁶ Recent surveys by the CDC revealed that approximately 33% of those with history of IVDA age 18-30 are infected and 70-80% of older individuals with history of IVDA are infected.² A summary of risk factors is shown in *Table 2*.

SYMPTOMS & TIMING OF INFECTION

Symptoms will vary between patients and typically only occur in acute infections. Most are not likely to prompt a medical visit as they can be mild, vague and are typically self-limited. Another consideration is that a large number of patients now acquiring acute Hepatitis C are IV drug users and symptoms can mimic opiate withdrawal. Patients in this population are frequently uninsured or underinsured, which is another barrier to presentation for care. Distrust of the medical profession can also exist in these patients. Symptoms include fever, fatigue, dark urine, clay-colored stool, abdominal pain, loss of appetite, nausea, vomiting, joint pain and jaundice.² Approximately 20-30% will have experienced fatigue, abdominal pain, loss of appetite or jaundice. The range in which patients experience symptoms from time of infection is 2-24 weeks; however, most symptoms occur between 4-12 weeks of infection.² Because of the nature of these symptoms, the fact that they can mimic other more common diseases like gastroenteritis, influenza, etc., it is difficult to diagnose acute Hepatitis C.

TABLE 2:

Summary of risk factors for transmission of Hepatitis C

Higher Risk of Transmission	Lower Risk of Transmission
<ul style="list-style-type: none"> • IV Drug Abuse • Blood transfusion before 1992 	<ul style="list-style-type: none"> • Birth to a HCV + mother • History of chronic hemodialysis • History of needlestick or mucosal exposure • Incarceration • HIV+ men who have sex with men • Organ transplant prior to 1992 • Persistently elevated ALT • Recipient of clotting factor concentrate before 1987 • Sex with a HCV+ partner • Sexual contact where blood/ blood contact may occur • History of intranasal illicit drug use • Tattoos from an unregulated establishment

SCREENING

Screening has long been a standard with blood product donation and collection since its implementation in 1992, however, routine screening in other healthcare settings has undergone recent changes. Recommendations from several professional organizations and governing bodies are below.

The CDC recommends screening for people born between 1945-1965, anyone who has ever injected illegal drugs (even if it is only once), recipients of clotting factor concentrates made before 1987, recipients of blood or organ transplants before 1992, patients who have ever received long term hemodialysis, patients with known exposures to HCV, all patients with HIV infection, patients with signs of symptoms of liver disease and children born to HCV positive mothers.² The CDC notes routine testing is of uncertain need in recipients of certain tissues (corneal, musculoskeletal, skin, ova or sperm), non-injecting illegal drug users, those with tattoo or body piercing, persons with history of multiple sexual partners or sexually transmitted infections, or long term steady sex partners of HCV positive persons.² The CDC recommends against routine testing in the following populations when they are without risk factors: Healthcare care, emergency medical and public safety workers, pregnant women, household (nonsexual) contacts of HCV positive patients, and the general population.²

The USPSTF recommends screening patients at high risk (those with any risk factors in table above) and also those born from 1945-1965. This grade B recommendation was published in 2013 and the USPSTF is currently in the process of updating this recommendation.¹⁸

Some states have passed laws surrounding screening for Hepatitis C. The Commonwealth of Pennsylvania passed a law in 2016 requiring any individual born between the years of 1945 and 1965 who receives health services as an inpatient or who received primary care services in an outpatient setting be offered a Hepatitis C screening test or Hepatitis C diagnostic test.¹⁹ Other states including Connecticut, Massachusetts and New York have similar screening laws for patients in that population.

Pregnant women are a special population that requires more discussion. Without risk factors, screening is not recommended, however in certain geographic locations, especially those with high incidence of Hepatitis C, more consideration may be necessary. The CDC reported that rates of HCV infection in women of childbearing age (15-44) increased 22%, and hepatitis C testing of children age <2 increased 14%.² Overall births to mothers with HCV infection rose from 0.19% to 0.32% based on 2014 data. Vertical transmission to infants born to HCV-positive mothers is between 5-6%. Although these numbers are very low, screening based on individual patient history is important and should not be ignored.²⁰ Ultimately, having a high index of suspicion and screening patients who participate in behaviors placing them at high risk for Hepatitis C is essential. This applies to both pregnant and non-pregnant patients. Data from the National Notifiable Diseases Surveillance System compiled in a study in the *Annals of Internal Medicine* reported an increase in HCV infection of reproductive age women from 16,000 in 2006 to 31,000 in 2014.²¹

DIAGNOSIS

The screening test of choice is the anti-Hepatitis C antibody (sensitivity of 95%, specificity of 99%, positive likelihood ratio of 95, and negative likelihood ratio of 0.05).¹⁶ It can detect the antibody 4-10 weeks after exposure and detect >97% of cases by 10 weeks after exposure.² If the result is positive, then confirmatory testing should be pursued with a Hepatitis C RNA viral load by PCR with a genotype. HCV RNA can be detected 2-3 weeks after initial infection. If the result is negative and there is significant suspicion for exposure within the previous 6 months, HCV RNA should be ordered every 4-8 weeks, or repeat antibody testing can be performed at 12 weeks. If the HCV antibody is positive, but the HCV RNA is negative, the patient is considered to not have HCV infection.¹⁷

In patients with a positive HCV RNA test, but negative anti-Hepatitis C antibody, an acute infection is diagnosed. Treatment is not recommended for patients with an acute infection, however the HCV RNA viral load should be monitored for 6 months to evaluate for spontaneous clearance.¹⁷ The process of screening and potential outcomes are demonstrated in *Figure 1*.

ASSESSMENT

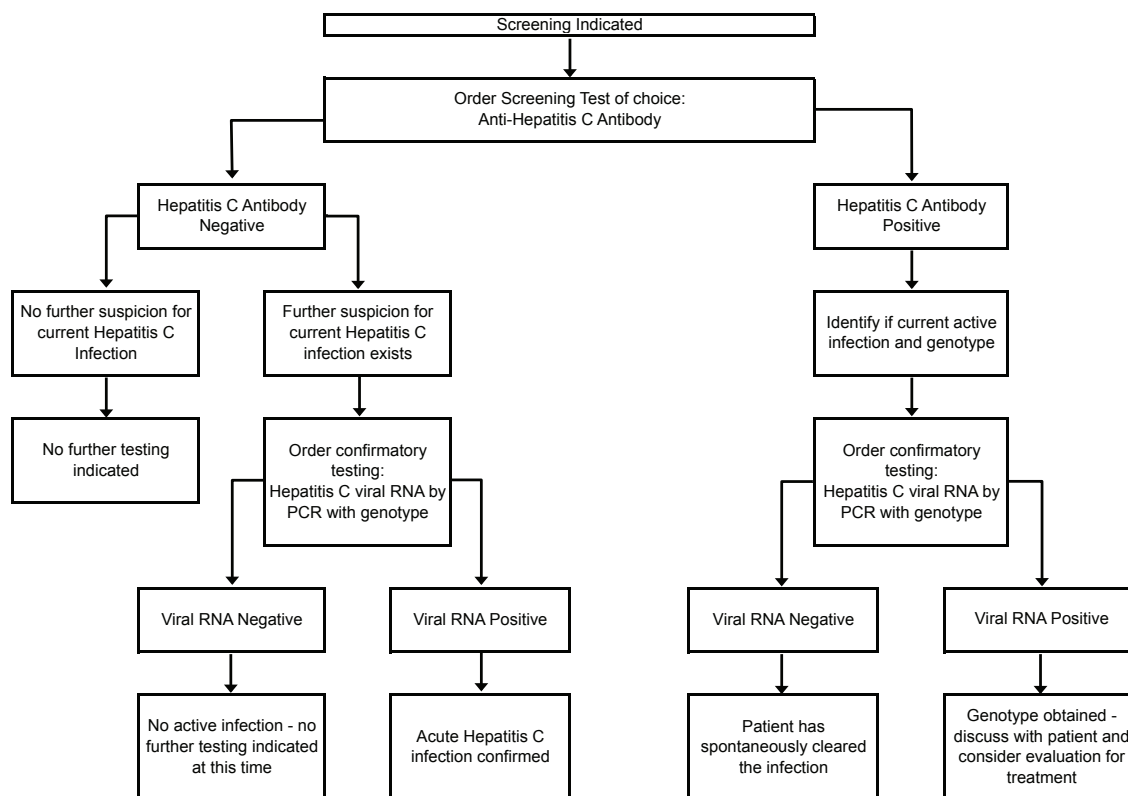
Once the diagnosis is made, assessing the level of fibrosis and/or cirrhosis is an important step in determining the pathway to treatment. The preferred method is a liver biopsy, however biomarkers can be an acceptable alternative. There are a number of different biomarkers, including several cytokines, collagens, collagenases, etc. that mirror the breakdown of hepatic extracellular matrix. These can be used in certain combinations to predict progression, however they are not widely available and there is a paucity of confirmatory and comparison studies. Because of the rapid growth of new developments in biomedicine and biotechnology, biomarkers provide interesting future options once studies are done to determine their effectiveness in predicting hepatic damage.⁵⁰ The recommendations for grading and treatment are based on the Metavir scoring system, which scores fibrosis from 0-4 points, and recommends pursuing treatment based on a score of 2 or greater.¹⁶ Scores are assigned as follows: 0 for no cirrhosis, 1 for minimal scarring, 2 for scarring beyond areas containing blood vessels, 3 for bridging fibrosis with connections to other areas of fibrosis and 4 for cirrhosis or advanced scarring.¹⁶ These patients should also be assessed for Hepatitis B, HIV and other conditions that can cause more rapid fibrosis as mentioned in the section entitled "risk factors for disease progression" above. Patients with HCV infection should also be immunized for Hepatitis A and B if not already fully vaccinated and have no history of infection.¹⁶

TREATMENT

All patients with chronic HCV infection should be considered for treatment based on genotype, degree of fibrosis, prior treatment, comorbidities and potential adverse effects.¹⁷ The goal of treatment is to reduce all cause mortality and hepatic-associated complications. Success of treatment is evaluated by repeat measurement of HCV RNA. A sustained viral response (SVR) is defined as absence of HCV RNA on PCR testing 24 weeks after

FIGURE 1:

The process of screening and potential outcomes



completion of treatment and is associated with a 99% chance to be HCV negative in long term follow up. Factors contributing to higher rates of SVR include patients younger than 40-45,²² genotypes 2 and 3, lower viral load²², being treated with a statin^{2,4} and African American race.²² Factors contributing to lower rates of SVR include advanced fibrosis²² and concurrent diabetes mellitus.²⁵ It should be noted that some of these align with the risk factors for disease progression, as African American patients and those diagnosed before age 40 have slower rates of progression and higher rates of SVR. In contrast patients with diabetes and other comorbidities have faster rates of progression and lower rates of SVR.

Treatment candidates include those who are 18 years of age or older, are able and willing to adhere to treatment, have elevated AST and ALT levels and have a Metavir score of 2 or more.¹⁶ Treatment has traditionally been managed by specialists, however, new studies are showing that treatment success rates are similar between specialists and adequately trained primary care providers. A study published in the *Annals of Internal Medicine* in 2017 enrolled 600 patients and had them follow with a specialist, PCP or nurse practitioner.²⁶ All providers underwent the same 3 hour HCV training program. SVR overall were 85-90% and similar among all provider groups, with follow up being greatest with the PCPs (63%) and NPs (74%) compared to the specialists (56%).²⁶ Adverse events were similar among all groups and consistent with previous safety trials. This study suggests that HCV treatment can

safely and effectively provided by appropriately trained primary care physicians and that the patients are more likely to complete follow up.

Interferon and Ribavirin were long-time mainstays of treatment, however had significant associated complications. Ribavirin has a black box warning for hemolytic anemia, can worsen cardiac disease, and has significant teratogenic effects.^{47,48} The teratogenic effects are so serious that women taking the drug and who were partners of men taking the drug were required to have 2 forms of reliable contraception. Interferon caused serious adverse effects including development of life threatening neuropsychiatric, autoimmune, ischemic and infectious disorders.⁴⁹

However, new direct acting antiviral medications, ledipasvir, sofosbuvir, glecaprevir, pibrentasvir, velpatisvir, and voxilaprevir have been approved for the treatment of Hepatitis C. These new agents are used in combination with one another and are all oral agents. They have excellent cure rates, lower side effect profiles and increased ease of use. However, there is significant cost associated with these newer regimens. As these medications are oral tablets and are taken daily, compliance is much easier to attain. In addition, side effect profiles are significantly better than previous medications, as the major side effects are nausea, headache and fatigue. Once the medication is prescribed, the patient takes it daily as prescribed and follows up for monitoring as below. A comprehensive list of approved medication combination pills as of January 2018 is shown in *Table 3*. A summary of the most common side effects of these medications is found in *Table 4*.

TABLE 3:

Approved medication combination pills as of January 2018

MEDICATION & ADMINISTRATION	GENOTYPE	PATIENT SELECTION & TREATMENT LENGTH	SUSTAINED VIRAL RESPONSE (SVR)	ESTIMATED COST
Ledipasvir-sofosbuvir (1 oral tab daily)	1	TNP ^{27,28,29} : 8 weeks if viral load <6 million and no cirrhosis, 12 weeks if viral load > 6 million and/or cirrhosis TEP ³⁰ : 12 weeks	>95% 95%	\$37,800 per 4 weeks
	4	TNP, TEP ^{41,42} : 12 weeks	95%	
	5	TNP, TEP ⁴² : 12 weeks	95% (N=41)	
	6	TNP, TEP ⁴² : 12 weeks	96% (N=25)	
Sofosbuvir-Velpatasvir (1 oral tab daily)	1	TNP ^{31,32,33} : 12 weeks regardless of cirrhosis TEP ^{31,32,33} : 12 weeks regardless of cirrhosis	98-99% 98-99%	\$29,900 per 4 weeks
	2	TNP ^{31,36} : 12 weeks regardless of cirrhosis TEP ^{31,36} : 12 weeks regardless of cirrhosis	98-99% 97%	
	3	TNP ^{31,36} : 12 weeks regardless of cirrhosis TEP ^{31,36} : 12 weeks regardless of cirrhosis	98% (93% if cirrhosis) 91% (89% if cirrhosis)	
	4	TNP, TEP ³¹ : 12 weeks regardless of cirrhosis	100% (N=116)	
	5	TNP, TEP ³¹ : 12 weeks regardless of cirrhosis	97% (N=35)	
	6	TNP, TEP ³¹ : 12 weeks regardless of cirrhosis	100% (N=41)	
Glecaprevir-pibrentasvir (3 oral tabs once daily)	1	TNP ^{34,35} : 8 weeks without cirrhosis, 12 weeks with cirrhosis TEP ^{34,35} : same as TNP	99% 99%	\$15,840 per 4 weeks
	2	TNP ^{34,37,38} : 8 weeks without cirrhosis, 12 weeks with cirrhosis TEP ^{34,37,38} : same as TNP	98% Limited Data	
	3	TNP ³⁹ : 8 weeks without cirrhosis, 12 weeks with cirrhosis TEP ⁴⁰ : regardless of cirrhosis	95% 98% 96%	
	4	TNP, TEP ^{34,37} : 8 weeks without cirrhosis, 12 weeks with cirrhosis	93% (N=46) 99% (N=16)	
	5	TNP, TEP ^{34,37} : 8 weeks without cirrhosis, 12 weeks with cirrhosis	93% (N=27 total) 99%	
	6	TNP, TEP ^{34,37} : 8 weeks without cirrhosis, 12 weeks with cirrhosis	100% (N=30 total) 100%	
Sofosbuvir-velpatasvir- voxilaprevir (1 tab daily)	1-6	TEP with previous failure ⁴³ : 12 weeks	98%	\$29000 per 4 weeks

MONITORING & FOLLOW UP

Patients being treated for HCV should be monitored and assessed for compliance with therapy and adverse effects, including new or worsening psychiatric illness, and screened for alcohol and substance abuse at every visit.^{1,16} CBC, CMP, HIV, Hepatitis B status and pregnancy test (when appropriate) should be monitored initially and at week 4. HCV RNA viral load is recommended at week 4 of treatment and also at 12 and 24 weeks after treatment.¹⁷ Patients with resolved or inactive Hepatitis B are at risk for reactivation during treatment, which also requires consideration for screening/monitoring. Some experts have suggested monitoring HBV DNA levels during treatment, as increases in HBV DNA are the most likely finding of reactivation. If this were indicated, monitoring at weeks 4, 12, and 24 with other lab work would be reasonable. The risk of Hepatitis B reactivation and treatment should be discussed with patients on an individual basis.⁴⁴

LONG TERM OUTCOMES

Several studies have shown the long term outcomes with treatments discussed above are reducing morbidity and mortality. A prospective study published in *Gastroenterology* followed 1323 patients with cirrhosis for complications after treatment, which included direct antivirals as they became available and also previous interferon therapy. 5 year survival was 88.6%, with 50.5% achieving SVR. Achieving SVR lowered mortality (HR 0.27), lowered hepatic decompensation (HR 0.26) and lowered rates of hepatocellular carcinoma (HR 0.29).⁴⁵

Another study examining over 3004 patients from multiple countries, using phase 3 clinical trial data has shown that only 12 out of 3004 patients had detectable levels of HCV RNA at 24 weeks, after having SVR at 12 weeks. Seven were found to be a result of reinfection, with only 5 being the result of relapse (medication failure). This data shows that if SVR is achieved with the direct-acting antivirals, long term SVR is very likely to be achieved without relapse.⁴⁶

AUTHOR DISCLOSURES:

No relevant financial affiliations

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TABLE 4:

A summary of the most common side effects

	ADVERSE REACTIONS	CONTRAINDICATIONS
All Medications	Headache (11-31%) Fatigue (10-18%) Nausea (6-13%)	
Ledipasvir-Sofosbuvir	Weakness (11-31%) Myalgia (9%)	None
Sofosbuvir-Velpatasvir	Increased Lipase (>3x Upper Limit of Normal) (5-7%)	None
Glecaprevir-Pibrentasvir	Diarrhea (7%)	Coadministration of rifampin or atazanavir in Child's-Pugh Class C liver disease
Sofosbuvir-Velpatasvir-Voxilaprevir	Diarrhea (14%) Weakness (5%) Increased bilirubin (4-13%)	Coadministration of rifampin

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