Review

Clinical Evaluation of Chronic Hepatitis C and Indications for HCV Treatment

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Hepatitis C virus (HCV) is the most common cause of liver cirrhosis in the United States. If untreated, HCV can lead to death from complications of liver failure or hepatocellular carcinoma, making screening imperative in high-risk patients. Established risk factors for HCV infection include injection drug use, receipt of blood transfusion or organ transplantation prior to 1992, and hemodialysis. Recent evidence has demonstrated that those born between 1945-1965 are additionally at high risk for HCV acquisition and should undergo one time screening. Once diagnosed, consideration for treatment should be based on patient motivation, concurrent medical co-morbidities, degree of liver injury, and risk of progression to cirrhosis. Therapy may also be indicated in patients with extra-hepatic manifestations of HCV.
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INTRODUCTION

Hepatitis C virus (HCV) is a global public health problem, with an estimation of 180 million people infected worldwide.[1] In the United States (U.S.), HCV is the number one cause of liver cirrhosis and the leading indication for liver transplantation, and the Center for Disease Control and Prevention (CDC) approximates that 3.4-4.9 million people in the U.S. may be infected.[2,3] Estimates indicate that the HCV screening rate in the U.S. ranges from 40.6 to 63.5%.[4] Morbidity and mortality from HCV is primarily due to cirrhosis related complications, including esophageal variceal bleeding, ascites, hepatic encephalopathy and hepatocellular carcinoma (HCC), and it has been estimated that mortality related to HCV infection, secondary to will continue to increase over the next two decades.[9] In addition to the impact on patient mortality, HCV and its associated sequelae also have a significant economic burden. In 1997, an estimated $5.46 billion was spent on management of HCV infection.[5] Another study demonstrated that in managed care plans, costs in HCV positive individuals was nearly 4 times that of HCV negative patients.[6] Liver cirrhosis and primary liver cancer secondary to HCV often occurs over a period of decades, and HCV infection may go unrecognized prior to development of these complications.[7] Therefore, early detection and treatment of the disease is imperative. This review summarizes the management of HCV, regarding the appropriate population to screen, diagnostic evaluation and indications for treatment.

Indications for Screening

HCV infection screening should be performed in patients who have a history of potential exposure to the virus and in those who have an identifiable risk factor.[8] As HCV infection is transmitted most commonly through blood-to-blood contact with an infected individual, all persons who may have had such exposure should be tested for HCV. This is particularly important for healthcare workers who may have been exposed to HCV contaminated blood through a needle stick injury.

In the US, the most common risk factor for HCV acquisition is injection drug use, and therefore testing is recommended for individuals with a history of intravenous drug.[7] Additionally, those who have received a blood or blood product transfusion or undergone organ transplantation before 1992 should also be tested, since prior to 1992 assays to detect HCV antibodies were unavailable.[9] Additional risk factors associated with HCV infection include unexplained elevations of liver transaminase levels, prior history of hemodialysis, birth from an HCV positive mother, or presence of human immunodeficiency virus (HIV) infection.[10,11]

In 2012, the Centers for Disease Control and Prevention (CDC) established new recommendations stating that patients born between 1945-1965, even without other identifiable risk factors, should be screened for HCV on one occasion.[12] These recommendations were based on a systematic review of prior studies, which demonstrated that nearly 75% of HCV infected patients in the U.S. are comprised of this birth cohort. The reason for the high prevalence of HCV in this population is unclear, but has been speculated to be from blood-to-blood transmission during routine medical care.[12]

Recommendations from the U.S. Preventative Task Force regarding in whom to perform HCV screening are outlined in **Table 1**.

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Table 1. Persons in whom HCV screening is recommended.

Persons who have injected illicit drugs in the recent and remote past, including those who injected only once
Persons with conditions associated with a high prevalence of HCV infection including: o Persons with HIV infection o Persons with hemophilia who received clotting factor concentrates prior to 1987 o Persons who have ever been on hemodialysis
Persons with unexplained abnormal aminotransferase levels
Prior recipients of transfusions or organ transplants prior to July 1992 including: o Persons who were notified that they had received blood from a donor who later tested positive for HCV infection o Persons who received a transfusion of blood or blood products o Persons who received an organ transplant
Children born to HCV-infected mothers
Health care, emergency medical and public safety workers after a needle stick injury or mucosal exposure to HCV-positive blood
Persons born between the years 1945-1965

Screening Methods

In individuals who meet the recommended criteria, screening should be performed with serologic testing of HCV antibody, a highly cost-effective method which has 97% specificity and sensitivity ranging from 97-100%.[13] If HCV antibody testing is positive, confirmation should be performed with testing of an HCV quantitative RNA level.[14] This is primarily because HCV antibody testing may be positive in those with prior exposure who have spontaneously cleared the virus.

Confirmatory testing with HCV RNA level is also recommended in certain patient groups with a negative HCV antibody. For example, in patients with acute HCV exposure, antibody testing may not be detectable until 8-12 weeks afterwards. In such instances, HCV RNA testing is recommended since it can become detectable within 2 weeks after exposure. False negative HCV antibody testing can additionally occur in immunocompromised patients, even with active infection. Confirmation of a negative HCV antibody in such individuals with RNA testing is also recommended.[14]

Additional Testing After Confirming Diagnosis

Once the diagnosis of HCV has been confirmed, additional testing is necessary. Of primary importance is HCV genotype testing, since the appropriate treatment regimen is based on the HCV genotype. If a liver function panel has not been performed, it is recommended to determine the degree of hepatic inflammation. Furthermore, elevation in the total bilirubin or a low serum albumin level may indicate liver dysfunction. Checking a complete blood count is also recommended as presence of thrombocytopenia may be marker of portal hypertension.

In an individual with abnormal liver transaminase levels, blood testing should be performed to rule out other etiologies of elevated liver function tests. This includes testing for hepatitis B surface antigen, iron, transferrin and ferritin level to evaluate for hemochromatosis, anti-nuclear and anti-smooth muscle antibody to assess for autoimmune hepatitis.

In patients who will be initiated on interferon-based therapy, a creatinine level should be checked to assess treatment candidacy and determine if medication dosage adjustments are needed. Additionally, given the possibility of interferon induced thyroid disease, a baseline thyroid stimulating hormone should also be tested.

Within the past few years, testing has become available for the IL-28B genotype, which can help determine the response to interferon-based therapy in patients with genotype 1 HCV.[15] However, as newer treatments have been developed which depend less on interferon, the role of IL-28B testing has been given less importance.

Role of Liver Biopsy

During the era of interferon-based therapy, a liver biopsy was recommended in HCV genotype 1 infected patients to stage the degree of liver fibrosis, and therefore determine whether the benefits of treatment are greater than the associated risks. This was based on the notion that treatment would be required for 48 weeks, side effects may have been difficult to tolerate, and the success rate was approximately 40% for achieving cure.[14] With the advent of therapy utilizing direct acting antiviral agents, success rates have risen significantly, while duration of therapy has decreased. Subsequently, a liver biopsy has become less important in deciding whether the benefits of treatment outweigh the risks. A liver biopsy is still useful for patients in whom another underlying disease is suspected, such as autoimmune hepatitis or non-alcoholic steatohepatitis.

Indications for treatment

The treatment goals for antiviral therapy for HCV are to eradicate the virus (sustained virologic response, SVR) in order to achieve biochemical improvement (normalization of alanine aminotransferase) and histologic improvement (> 2 point improvement in necroinflammation with no worsening of fibrosis).[13] Meeting these goals has been shown to prevent the long -term complications of cirrhosis and hepatocellular carcinoma.[15,16] Determining who to treat and when to treat are key clinical issues. General treatment criteria are noted in **Table 2**.

Table 2. Indications for treatment.

18 years of age or older
Detectable serum HCV RNA
Liver biopsy with chronic hepatitis and/or significant fibrosis
Compensated liver disease
Acceptable hematologic and biochemical laboratory parameters
Adherent to medical and treatment recommendations
No psychiatric or medical contraindications to treatment

After acute infection, HCV persists in 55-85% with persistent viremia and ongoing liver inflammation. Of those chronically infected, the slow development of fibrosis and cirrhosis over 2 to 3 decades occurs in up to 25% of individuals.[17] Risk factors for progression include co-

infection with HIV, HBV, significant alcohol ingestion, male gender, and obesity.[18-21]

Although theoretically, all patients with detectable viremia are candidates for treatment, determination of those at greatest risk of progression is the more measured approach to selection of patients for treatment. Liver biopsy is the main modality used to stage degree of fibrosis and those with greater than stage 1 fibrosis are deemed appropriate candidates for therapy.[13] With the introduction of new non-interferon based therapies that will have better tolerability, a broader population of eligible patients may change these criteria. Other modalities for the assessment of fibrosis such as serum markers of fibrosis (Fibrotest, Fibrosure) or newer technologies such as transient elastography have been shown to also have utility in staging.[22,23]

Acute Hepatitis C

The majority of patients with acute HCV are not diagnosed as many are asymptomatic or have nonspecific constitutional symptoms. If exposure is confirmed, spontaneous clearance can occur in up to 50% and will usually clear within 12 weeks of infection.[24,25] Symptomatic presentation predicts a better chance of clearance, however if spontaneous clearance does not occur, treatment is indicated as earlier treatment with interferon has shown excellent response rates >80%.[26]

Normal Alanine Transaminase (ALT)

Although more recent data suggest that normal ALT should be defined as ALT <30 IU/ml for men and 19 IU/ml for women,[27] patients with normal ALT (as more typically defined as less than less than 40 IU/ml) can have significant fibrosis (30%) or even cirrhosis (1.3%).[13] Therefore appropriate staging and assessment of fibrosis should be considered and therapy initiated even with persistently normal ALT.

Extrahepatic manifestations of HCV

Several extrahepatic manifestations of HCV infection have been described including cryoglobulinemic vasculitis, membranoproliferative glomerulonephritis, porphyria cutanea tarda, B-cell lymphoproliferative disorders, and lichen planus, amongst others.[28] The most common extrahepatic manifestation of HCV, cryoglobulinemia has been reported in 25-30% of HCV infected individuals and alternatively 90% of those with mixed cryoglobulinemia are HCV positive.[29,30]

Immune mediated clonal expansion of B cells and production of IgM with rheumatoid factor activity which then binds to HCV to form an immune complex.[31] Treatment is not indicated in for asymptomatic cryoglobulinemia, but the development of palpable purpura, arthralgias, renal disease, neuropathy or other clinical sequelae would necessitate consideration of therapy. Interferon therapy with ribavirin (if tolerated based on renal function) resulting in viral suppression or eradication results in high rates of resolution of cryoglobulinemia (> 70%) related complications. If interferon therapy is not feasible due to tolerability, other therapies such as cyclophosphamide, rituximab, corticosteroids, plasmapheresis may be needed.

B cell non-Hodgkin lymphomas have also been reported in association with HCV due to chronic antigen stimulation leading to monoclonal malignant proliferation. One meta-analysis found a strong association with an odds ratio of 5.70, particularly in countries with high prevalence.[32] Antiviral therapy has been shown to regress with therapy [33] and may prevent lymphoma development in HCV infected patients, although more research is needed in this arena.

CONCLUSIONS

Hepatitis C infection remains a major cause of liver morbidity and mortality leading to high rates of cirrhosis and hepatocellular carcinoma. Recent screening recommendations focus on both risk based assessment as well as age based screening of baby boomers. Once positively identified with HCV, treatment is currently indicated in individuals who have significant liver injury, suggesting a higher risk of long-term progression risk. Weighing the risks and benefits of treatment will change in the near future as new treatment regimens become shorter and easier to tolerate and treatment indications may be broadened.

CONFLICT OF INTEREST

None.

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