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**INTRODUCTION**

It has been a mere 10 years since a portion of the genome of the hepatitis C virus (HCV), the infectious agent responsible for most cases of post transfusion hepatitis was sequenced. The discovery in 1989 was followed by the development of tests to detect anti-HCV antibodies, facilitating the screening of potential blood donors. As a result, the number of new cases of HCV infections has decreased dramatically from an estimated 180,000 cases in the mid-1980s to 28,000 cases in 1995\(^1\). Despite this reduction in the number of cases of acute infection, HCV infection remains a significant health concern in light of the tendency for most patients to develop asymptomatic, chronic HCV infection. It is estimated that approximately 4 million (1.8%) Americans are currently infected with HCV\(^2\). Chronic HCV carriers are at higher risk for cirrhosis, end stage liver failure and hepatocellular carcinoma. Furthermore, since chronic HCV individuals remain viremic, they are capable of transmitting the infection to others. In recognition of the scope of HCV associated disease, the following review is provided. Our intent is to provide the with an overview of HCV infection, with special mention of HCV infection in the pregnant patient.

**VIROLOGY**

Hepatitis C virus is a single-stranded RNA virus approximately 9.5 kilobases in length. Although, the entire viral genome has been sequenced, the virus still has not been visualized. Six different genotypes (1-6) and three sub-types (a, b, c) of HCV exist worldwide. In the United States, genotype 1 is responsible for the majority of infections. Although all genotypes are pathogenic, certain genotypes may be more responsive to treatment than others\(^2\).

HCV transmission occurs principally via large or repeated exposure to the blood of infected individuals. Prior to routine screening of blood donors (1992), transfusion related transmission was responsible for the majority of new cases. Solid organ transplantation prior to HCV screening of donors was also responsible for transmission of the virus. Today, illegal injectable drug use is the factor most commonly identified in newly diagnosed cases of HCV infection. The majority of individuals with HCV infection will possess a history of parenteral exposure. However, in a small percentage of infected individuals, no clear mechanism for viral acquisition can be determined. Non-parenteral transmission via vaginal secretions, saliva, urine and semen can occur, although the risk for such transmission appears to be small\(^3,4\). HCV is not transmitted through casual contact. Furthermore, epidemiological studies of non-sexual, household contacts of HCV infected individuals suggest that horizontal transmission rarely occurs\(^5\). In some instances, horizontal transmission between sexual partners may occur. Fortunately, this mode of transmission appears to be rather ineffective.

The incubation period for newly acquired HCV infection is may range from 2 weeks to 6 months (average 6-8 weeks)\(^1\). During this incubation period active viral replication is occurring. Viral RNA may be detected within 1-2 weeks of acute infection\(^6\). Subsequently, a host immune response leads to the formation of immunoglobulins directed at the HCV. These anti-HCV antibodies can be detected using available assays within 4-6 weeks of an acute infection. The development of anti-HCV antibodies does not indicate resolution of the acute infection nor does it imply protection from the virus. HCV exhibits a high of mutation, which allows the virus to escape neutralization by preexisting antibodies. This viral property is ascribed to a hypervariable region (HVR1) within one of the HCV envelope proteins. This "viral plasticity" leads to the production of numerous "quasispecies" and is the mechanism by which HCV escapes antibody clearance and promotes chronic infection\(^6\).
CLINICAL DISEASE
In the US, 20% of cases of acute hepatitis are caused by HCV. It is estimated that over 90% of post-transfusion hepatitis are due to HCV infection. Since the advent of blood screening for HCV infection, the frequency of post-transfusion infection has decreased dramatically. However, intravenous drug use remains a significant route for HCV acquisition. Because of its predisposition for chronic infection, HCV for nearly 50% of cases of chronic hepatitis in adults and is the leading cause of end-stage liver disease requiring liver transplantation.

Following acute HCV infection, most patients remain asymptomatic; only 20% becoming icteric and less than 10% becoming seriously ill. Anti-HCV antibodies are present in 70-80% of patients at the onset of symptoms; 90% will develop antibodies within 3 months of onset. Acute infection gives way to chronic infection in approximately 85% of cases. In 2/3rds of these cases, chronic infection, defined by persistently elevated alanine amiotransferase (ALT) levels more than 6 months after the onset of infection, ensues. As with acute infection, most patients with chronic HCV infection are asymptomatic. In those with symptoms, non-specific fatigue is the most common complaint. Chronic HCV infection shows a tendency towards cyclic bouts of hepatitis associated with waxing and waning ALT and viral RNA levels.

The progression to cirrhosis is not an inevitable consequence of chronic HCV infection. The tendency to more severe disease, manifested by persistent viremia, ongoing hepatitis, and cirrhosis may in part be related to the viral serotype. By 20 years, approximately 20-35% of patients with chronic HCV infection will have progressed to cirrhosis. After 30 years, 20-25% will have developed hepatocellular carcinoma (HCC), almost all of whom also have cirrhosis.

A number of extrahepatic manifestations of HCV infection have been described. There are good data in support of an association among HCV infection and essential mixed cryoglobulinemia, membranoproliferative glomerulonephritis, and porphyria cutanea tarda. An association between HCV infection and Mooren corneal ulcers, autoimmune thyroiditis, Sjogren Syndrome, lichen planus and idiopathic pulmonary fibrosis has also been suggested although the evidence in support of this is weak.

DIAGNOSIS
Most patients infected with acute and chronic HCV infection have no clinical evidence of hepatitis. Frequently, the diagnosis follows the detection of anti-HCV antibodies drawn prior to blood donation or during the course of evaluation for an unexplained transaminase elevatation. In other individuals, HCV infection remains undiagnosed until the patient presents with late sequelae of chronic HCV infection, e.g. cirrhosis, bleeding esophageal varices, ascites, encephalopathy. Presently, universal screening for HCV infection is not recommended. Instead, screening should be provided to any patient possessing risk factors for HCV infection (Table 1).

The initial diagnostic test for suspected HCV infection involves an assay to detect for the presence of anti-HCV antibodies. The ELISA assay in current use has been modified numerous times since its introduction in 1990. The current generation ELISA assays test for antibodies to 4 viral antigens and has superior sensitivity and specificity (>95%). The assay cannot distinguish between IgM and IgG antibodies and thus cannot differentiate between recent or remote infection. False positive results may result from cross-reacting antibodies or in the setting of autoimmune disease. False negative results may occur in cases of late seroconversion, decreased antibody titers, and during periods of seronegativity.

Following a positive ELISA assay, a supplementary assay is typically performed to confirm the diagnosis. In high risk patients with persistent elevations of ALT, this may not be required. The Recombinant Immunoblot Assay (RIBA) is the most widely used confirmatory assay and, like the ELISA detects the presence of preformed anti-HCV antibodies. The RIBA is considered more sensitive and specific than ELISA testing. However, the assay is more expensive, less available, and more time consuming to perform, thereby limiting its usefulness as a primary screen. Following a positive ELISA, anti-HCV antibodies will be detected in 70-100% of high-risk patients by RIBA. In contrast, less than 50% of low-risk patients will test positive by RIBA. Conversely, 1-5% of patients with a negative ELISA will test positive by RIBA.

The ELISA and RIBA assays detect for the presence of preformed antibodies; neither test for the presence of the virus. Using PCR techniques, assays are now available that can detect the presence of HCV particles. The ability to detect HCV particles in the blood has several theoretical advantages. HCV RNA is present in the blood shortly after acute infection, predating the development of anti-HCV antibodies by 2-4 weeks. Viral detection would allow for the earlier detection of acute HCV infection. Furthermore, quantification of HCV levels may help better define the infectious risk of individuals.
Finally, because of the relationship between disease activity, viral replication, and Hepatitis C viremia, assessing the level of HCV-RNA may prove valuable in monitoring the response to experimental treatment protocols. The expense, limited availability, and lack of standardization in assay methodology renders HCV-RNA quantification to investigational status. HCV RNA quantification is not recommended as a primary or confirmatory diagnostic test at this time but instead should be reserved for cases of suspected HCV infection with conflicting anti-HCV serology. Patients with confirmed HCV infection should undergo periodic transaminase assessment. Further interventions might be considered for patients with chronic HCV infection who demonstrate persistent transaminase elevations. There is little correlation between serum transaminase values and the degree of histologic severity of hepatitis. Therefore, in order to evaluate the severity of ongoing hepatitis in these patients, HCV RNA quantification and/or liver biopsy are often considered prior to undergoing therapy.

**TREATMENT**

Studies examining the benefits of medical therapy in both acute and chronic HCV infection exist. In both clinical situations, beta interferon is the most frequently used drug. In patients with acute HCV infection, early treatment with interferon has been associated with an improved rate of ALT and viral level reduction versus no treatment. It remains to be determined if early treatment of all patients with acute HCV infection is preferable to selective therapy for patients with chronic HCV infection. Furthermore, it is unproven that treatment of acute HCV alters the long-term disease progression. Interferon therapy is currently approved for the treatment of chronic HCV infection. Treatment is typically reserved for patients felt to be at the greatest risk for progression to cirrhosis as determined by persistent laboratory abnormalities (ALT and HCV RNA elevations) with/without histologic abnormalities on liver biopsy. Although an improvement in ALT and viral levels is seen in up to 50% of patients during treatment, only 25% will show a sustained remission after one year. It still remains to be established if this short term remission modifies the long-term disease progression. The disappointing rate of long-term remission in HCV positive patients treated solely with interferon have prompted a number of studies evaluating the benefits of interferon in combination with other therapies. Although several have been studied including corticosteroids, ursodiol, and thymosin, the anti-viral agent ribavirin (Virazol) combined with interferon have yielded the most encouraging results in preliminary, experimental trials.

**HCV INFECTION AND PREGNANCY**

Universal screening of all pregnant women is not currently recommended; however, patients with defined risks for HCV infection should be offered screening (Table 1). Documented maternal HCV infection is not a contraindication to pregnancy; the presence of HCV infection does not require any alteration in the routine antepartum or intrapartum care. Known anti-HCV positive women considering pregnancy should be advised of the 5-10% risk of transmitting the infection to their infant. Because of the frequent coexistence and common risk factors of HCV and HIV, HIV screening should be offered to all anti-HCV positive individuals. Knowledge of coexistent HIV infection is important considering some studies have shown a higher rate (15-40%) of fetal transmission of HCV in anti-HCV positive women co-infected with HIV. Fetal infection is highly unlikely in women who remain HCV RNA negative. Therefore, periodic assessment of maternal HCV RNA throughout pregnancy may assist the clinician in better defining the individual maternal risk for vertical transmission. Infants born to anti-HCV positive women should be screened for HCV infection after 12 months of age.

**PREVENTION**

In the absence of an effective therapy or vaccine for HCV infection, minimizing the number of new infections is the primary means to control the spread of the virus. The benefits of blood and organ donor screening have been realized in a sharp reduction in the number of new cases of HCV infection. Individuals may minimize their risks of acquiring HCV by following blood and body fluid precautions. High-risk behaviors with potential exposure to shared needles (e.g. IV drug abuse, tattooing) should be avoided. HCV is not spread via casual contact. Many individuals with chronic HCV infection are unaware they are infected. A risk-based HCV screening approach would serve to identify most infected individuals. Once identified, anti-HCV
positive individuals need to be made aware of their potential infectivity and informed of behavior modifications to minimize the risk of transmission to others. Infected individuals can be reassured that non-sexual, household transmission is rare and that horizontal transmission between sexual partners rarely occurs. No change in sexual practices is recommended for anti-HCV positive individuals in stable, mutually monogamous relationships. However, some couples may individually choose to modify their sex practices in light of the small potential risk for horizontal viral transmission. Anti-HCV positive patients with multiple partners should consider: 1) informing their partners of their HCV status; 2) reducing the number of sex partners; and 3) using latex condoms, despite the lack of data to confirm their efficacy in reducing HCV viral transmission. Anti-HCV positive individuals should clearly not donate blood, organs, tissue or semen. They should cover all skin wounds to avoid inadvertent spreading of infected blood. Household sharing of toothbrushes, razors or other items potentially contaminated with blood should be avoided. High-risk behaviors with the potential for needle sharing should be avoided. If IV drug use is continued, patients should be counseled to use sterile supplies and avoid sharing their paraphernalia with others.

CONCLUSION
The nature of HCV infection, with a tendency towards chronic infection ensures that it will remain a significant public health problem. Because of the paucity of symptoms, most affected individuals are unaware of the infection. Anti-HCV antibodies do not provide protection from the virus; consequently, most chronic carriers remain viremic and potentially infectious. HCV is transmitted most readily via blood, and as such presents an occupational hazard to health care providers exposed to blood from infected individuals. Non-parenteral transmission also occurs, although less efficiently. Infected individuals need to be made aware of the potential for horizontal transmission between sexual partners and vertical transmission to the fetus. Investigations continue into potential therapies that may alter the course of disease for patients with chronic HCV infection. Unfortunately, interferon therapy for chronic HCV infection rarely results in a sustained remission. The benefit of this remission on the long-term progression of HCV is undetermined. No vaccine for HCV exists; consequently, efforts aimed at decreasing the number of new cases of HCV infection are essential for controlling the rate of spread of the infection.

TABLE 1 Risk factors for infection with Hepatitis C Virus

1. Blood transfusion or solid organ transplant prior to July 1992
2. Clotting factor concentrate prior to 1987
3. H/O intravenous drug use
4. Patients on chronic dialysis
5. H/O sexually transmitted disease
6. Sex partners of persons with HCV infection
7. Following exposure to HCV antibody positive blood
8. Infants over 12 months old born to HCV positive women

DIAGRAM 1 Suggested algorithm for the management of HCV infection

- ELISA
  - positive
  - negative
  - STOP
- RIBA
  - positive
  - negative
  - STOP
- ALT
  - Abnormal
  - normal
  - SERIAL ALTs
Consider HCV RNA, liver biopsy
Experimental
Tx Protocols
REFERENCES


For additional information on the world wide web go to the following:
Center for Disease Control (CDC) www.cdc.gov/ncidod/diseases/hepatitis/hepatitis.htm
Hepatitis Foundation International (HFI) www.hepfi.org
Hepatitis Information Network www.hepnet.com
www.epidemic.org

Source URL: http://www.obgyn.net/articles/hepatitis-c-infection-clinician%E2%80%99s-guide

Links: