Hepatitis C – Current Knowledge

Expires Sunday, June 30, 2019 Nursing Tamerou Asrat , M.D. F.A.C.O.G.

Objectives

1. Discuss the potential clinical impact of Hepatitis C infections and how patients are diagnosed and followed-up.
2. Describe the different ways in which the Hepatitis C virus can be transmitted between adults and to children through perinatal transmission and breastfeeding.
3. Discuss the potential treatment options for Hepatitis C infected individuals, the limitations of treatment, and the potential for an effective future vaccine or immunoglobulin.

Article

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Background and Healthcare Impact:

Many different viruses can lead to injury of liver cells producing hepatitis. Some of these are considered primary hepatitis viruses whereas others may produce hepatitis as part of their overall infection. For the primary hepatitis viruses, for years only two were distinctly known and were called Hepatitis A and Hepatitis B. Everything else was labeled non-A non-B hepatitis. In 1989, Choo and Kuo identified an RNA viral strand that was felt to be the cause of non-A non-B hepatitis. This RNA virus was soon labeled Hepatitis C (HCV). Since the discovery of the Hepatitis C virus, several distinct genetic variants have been identified based on different nucleic acid sequences.

Currently, 7 major genotypes exist and most of these have numerous subtypes, which are labeled progressively “a”, “b”, “c”, etc. There are currently over 225 subtypes identified to date. Some studies have reported genotypes 8 through 11, but most authorities list these as primarily variants of genotypes 3 and 6. The most common genotypes in the United States, Western Europe, and Japan are 1a, 1b, 2a, 2b, 3a, 4a, and 6a. The most resistant to treatment is genotype 1. The hepatitis C virus has been classified as a separate genus to the flavivirus family. This RNA virus is approximately 9379 to 9481 nucleotides long and is 30 to 38 nanometers in diameter.

As more information is obtained on the Hepatitis C virus, the potential clinical impact of this disease is becoming apparent. Research showed that the majority of post-transfusion hepatitis was caused by Hepatitis C. The Centers for Disease Control estimates that more than 150,000 new cases occur per year in the United States alone (mostly now related to substance abuse). Based on current information, it is estimated that there are over 200 million carriers worldwide, with approximately 4 million in the United States. Of acute infections, only 20% have symptoms (meaning 80% or 4 out of 5 have no symptoms and do not realize they were infected). Once infected, about 80% become chronic carriers and again they are usually asymptomatic.

Of these chronically infected HCV carriers, 75% will have elevated liver function tests, which means that 25% have normal tests but are still carriers. Chronic hepatitis C is slowly progressive, and it is estimated that 10% to 30% progress to cirrhosis after 20 years. Of those with cirrhosis, the risk of developing hepatocellular carcinoma is 2% to 5% per year. Therefore, the potential impact on healthcare in the United States and worldwide is enormous.

Furthermore, another difficulty that occurs in evaluating patients infected with this virus is that a viral marker antigen that denotes infectivity has not been identified. If one looks at hepatitis B, the presence of the hepatitis B surface antigen (HBsAg) denotes the possibility that a person is infectious. A similar antigen marker for hepatitis C does not currently exist. Infectivity is usually based on a positive HCV-RNA viral load.

Diagnosis:

In 2005, cell culture of hepatitis C became reality by 3 different research groups (Lindenbach et al, Wakita et al, and Zhong et al). This allowed every step of the viral lifecycle to be studied including viral entry into the body, replication, assembly of the virus, and release. What has made studying hepatitis C difficult is that there are essentially no animal hosts other than humans. There has been an attempt to develop a non-human primate host to study this, but research is primarily left to humans.

The structure of the virus is basically 11 proteins. There are 3 structural proteins, which are the core protein and 2 envelope proteins designated E1 and E2. There are 8 nonstructural proteins, which are primarily different enzymes. Most of these enzymes are used for replication of the virus once a host is infected. When hepatitis C enters the bloodstream, the envelope glycoproteins E1 and E2 bind to apolipoproteins (B, C1, and E) found on circulating cholesterol. The cholesterol that it attaches to is primarily VLDL and LDL. The full viruses then circulate through the bloodstream connected to these lipoproteins and are designated lipoviral particles. This allows the virus to have access to the liver making entry into the liver cell easier because of its connection to the cholesterol molecule. Once the virus is in the cell, the RNA viral genome is replicated using the cells resources. The virus is then reassembled again attached to lipoproteins and released back into circulation.

The diagnosis of an HCV infection primarily relies upon the detection of antibodies to the virus and identifying the nucleic acid of the virus by PCR testing (polymerase chain reaction). The laboratory workup primarily involves an ELISA screening test (enzyme linked immunosorbent assay) that looks for the presence of antibody to the virus. Currently, most labs now use a third generation anti-HCV ELISA test called an ELISA-3. This ELISA test, however, can have a very high incidence of false positive results, especially if used in a low risk population.

If a patient tests positive for HCV antibody, in the past, the next step was to evaluate by a RIBA test (recombinant immunoblot assay). This test was similar to the Western Blot Assay used in evaluating infection of HIV (human immunodeficiency virus). The RIBA test was a series of different antibodies to other aspects of the hepatitis C virus, and if positive, would suggest that the patient was infected or at least had been previously exposed (versus a false positive antibody screening test if the RIBA was negative). Unfortunately, the RIBA test is no longer available as of 2012. Therefore, a positive HCV antibody screening test is now confirmed by the more specific test of HCV-RNA viral detection by PCR. The problem associated with the RIBA test no longer being available, is that it is not fully possible to tell a patient (who has a positive HCV antibody screen test result and a negative HCV-RNA PCR test result) whether the positive antibody screen result was a false positive test versus the fact that an infection did occur, but the patient now has a negative viral load. Not being able to differentiate between these 2 possibilities could theoretically affect insurability.

The mean time period from an HCV infection to the development of an anti-HCV antibody response is 12 weeks but can take up to 6 months in some cases. Therefore, during an acute episode of hepatitis, the anti-HCV antibody test may be negative. Therefore, in evaluating a patient for acute hepatitis, the HCV RNA-PCR test should be ordered. If an individual is confirmed to be infected with HCV by a positive HCV-RNA viral load, they should have liver function tests performed along with hepatitis C genotyping. Additionally, a consultation with gastroenterology is recommended to determine if a liver biopsy is indicated and whether the patient is a candidate for treatment

(treatment based on the patient's current medical status and the genotype involved).

Transmission of HCV:

The spread of Hepatitis C is by a percutaneous or permucosal pathway. Therefore, the transmission between individuals primarily occurs in the following ways:

- Through Blood or Blood Products
- Through IV Drug Abuse
- Sexually
- Perinatal Transmission

The risk of HCV transmission between family members or sexual partners seems to be low at less than 1% (but is not reported to be zero). In a study by Nakashima et al, of over 1100 residents in an HCV endemic area of Japan, anti-HCV antibody was detected in 14% of the population. However, the positive rate amongst sexually active spouses was only 7% with half of those tested showing different serotypes. In a study by Bresters et al, all 50 heterosexual partners of HCV positive individuals were HCV-RNA and anti-HCV negative. The median duration of sexual relations was 13 years. Several other studies have also shown a low transmission rate by sexual activity (in the range of 1% or less). However, transmission can occur and it appears to be more common in patients with a history of multiple sexual partners. The sexual transmission rate to an uninfected person is also higher if the positive partner was infected through recurrent sources (IV drug abuse or multiple sexual partners).

This low transmission rate through sexual activity may be due to a low detection rate of the Hepatitis C virus in human secretions (other than blood). Therefore, the larger risk for HCV transmission in the population seems to stem from blood transmission such as transfusion with blood products, IV drug abuse, organ transplantation, or other external sources such as acupuncture, etc. As stated, the main area of concern when the transmission of hepatitis C was originally examined was its relation to post-transfusion hepatitis. Most studies revealed that the majority of post-transfusion hepatitis was caused by HCV. With the addition of anti-HCV testing and testing for the presence of virus by PCV of donated blood, the risk of developing post-transfusion hepatitis C infection is now less than 1 in a million units transfused. This testing of donated blood has markedly decreased the incidence of post-transfusion hepatitis in the United States. Though several papers report blood transfusion risks, the table below shows the approximant current risks of becoming infected through transfusion, per unit of blood transfused.

Table: Current estimated risks of transmitting infection per unit of blood transfused from Units that are negative in laboratory testing.

Hepatitis B	1 in 200,000 units transfused
Hepatitis C	< 1 in 1,000,000 units transfused
HIV I & II	< 1 in 2,000,000 units transfused

Immunoglobulins have been used in medicine for years to help prevent or reduce the risk of infections (for example

serum immune globulin, hepatitis B immune globulin, varicella zoster immune globulin, etc.). In addition, anti-D immune globulin (Rh-hyper-immuneglobulin) has nearly eliminated Rh sensitization in the United States. The safety of these products over the years has been excellent, despite the fact that these immune globulin products come from pooled plasma where some donors probably carry transmissible infections. In the mid 1990's, there were reports of Hepatitis C transmission following the administration of some brands of serum immune globulin. The frequency of this occurrence today is negligible and there has not been a reported case of HCV transmission in nearly 20 years.

Immune globulin production starts with a fractionation procedure that effectively removes most if not all potentially infectious agents. However, due to these reported HCV transmissions (from the over 20 years ago), most products (especially those used in the United States) add other purification steps such as a solvent-detergent treatment or a low pH treatment and pepsin. Therefore, Hepatitis C transmission with these products will hopefully stay non-existent in the future.

Lastly, nearly every study on patients with illicit drug abuse and addiction have found that about 70% to 75% of those infected with hepatitis C report that they had intravenous use. However, how the other 25% became infected (if intravenous drug use had not occurred) is uncertain. Newer research is suggesting that another mode of blood transmission might occur through the sharing of snorting utensils. Some of these patients (who chronically snort) develop sores in the nasal cavity, and this might lead to blood contamination of the snorting utensil. If this utensil is shared, then the blood of the infected user could gain access through the nasal mucosa of another user leading to possible infection.

Perinatal Transmission of HCV:

Vertical transmission from an infected mother to the infant does occur during pregnancy. Several hundred studies have been published on the topic of perinatal transmission during the past 15 years and the data is still not completely clear. When studies are combined, the rate of perinatal HCV transmission in pregnant patients who are anti-HCV antibody positive is about 5% (with a range of 0% to about 10%). These variations in percent transmission may be due to differences in those who are viral RNA positive in the bloodstream at the time of delivery and other factors. More recent data have determined that transmission primarily only occurs in patients who are HCV-RNA positive at the time of delivery (however, the laboratory that performs the PCR testing is important, because it is an extremely sensitive test). In addition, in patients who are HCV infected and are also HIV positive, the rate of perinatal transmission increases to a range of 15% to 25%.

The HCV positive carrier rate in studies of pregnant populations from Japan to Europe to the United States ranges from 0.5% to 3% (meaning 1 in 33 to 1 in 200 pregnant women are HCV antibody positive). It is important to understand that all babies born to women who are HCV-antibody positive are HCV-antibody positive at birth. This does not mean they are infected. The newborn's positive antibody test is caused by the mother's antibody that crossed the placenta. Mother's IgG antibodies can freely cross the placenta, but unfortunately, they are not protective to the newborn. Most of these newborns clear the antibody by 12 months of age. However, this maternal antibody can remain positive for up to 18 months following delivery in some uninfected children.

Another question that has not been fully answered is whether the virus can cross the placenta and infect the child prior to delivery. Most studies would suggest that this is not the case. Delamare et al tested the amniotic fluid obtained by genetic amniocentesis in 16 HCV-RNA positive women and in 15, the HCV-RNA probe was negative by PCR. The HCV-RNA was positive in one case at a very low level of 230 copies per ml of fluid. However, the amniocentesis procedure went through the placenta in a mother whose viral load was 340,000 copies per ml. This child and 9 others were tested at birth and all were negative for HCV-RNA. Therefore, the one positive amniotic fluid was probably caused by maternal blood contamination of the specimen. (Levels of HCV-RNA in the blood that are less than 10,000 copies per ml are considered low titers). PCR testing is very sensitive and can detect as few as 10 to 20 copies of virus in one milliliter of fluid. Therefore, a very tiny contamination can result in false positive results.

The Delamare report and most other studies suggest that the majority of perinatal transmission (when it occurs) takes place around the time of delivery. Because of this finding, the next question is whether the type of delivery affects this transmission rate. The majority of studies on this topic have reported that the mode of delivery did not seem to affect the perinatal transmission rate. However, it is important to note that nearly all of these studies did not separate the cesarean section group into elective cesarean prior to the onset of labor and those c-sections performed for obstetrical reasons after labor begins or membranes have been ruptured. One recent study by Gibb et al reported on the perinatal transmission rate in 441 mother-child pairs from Ireland and England using an estimation statistical approach. The perinatal transmission rate in 339 vaginal deliveries was estimated at 7.7% and the transmission rate in 54 non-elective c-sections was 5.9%. However, the transmission rate in 31 elective c-sections was 0%. Despite this finding, these percentages were not statistically different. On-

the-other-hand, the European Pediatric Hepatitis C Network reported on 1,787 mother-child pairs and the transmission rate for elective cesarean delivery was 7.3% versus 5.4% for the vaginal delivery / non-elective cesarean delivery group. Therefore, further studies are needed that analyze whether there is a difference between elective cesarean delivery and routine obstetrical delivery.

The final issue regarding pregnant women infected with HCV and their newborns is breastfeeding. No studies to date have ever proven transmission to a newborn through breastfeeding. Several studies have tested breast milk for the presence of HCV-RNA and most have not detected the virus. In a few studies, HCV-RNA was detected in breast milk, but at very low levels (of < 1000 copies per ml) and usually, this was only seen in colostrum. Furthermore, it is also uncertain whether the virus can withstand the elements of the intestinal tract. According to the American College of Obstetricians and Gynecologists and American Academy of Pediatrics, breastfeeding is not contraindicated in women who are HCV positive.

Treatment of HCV:

At the present time, there is no available Hepatitis C immune globulin or vaccine that can be used in preventing this infection. The current recommendations for treatment are still very complex. Therapy in the past was limited to interferon (or its variation) along with ribavirin and was dependent upon the patient's age, general state of health, risk of cirrhosis, likelihood of response, and life expectancy. In the past several years, numerous anti-hepatitis C anti-viral agents have been developed and marketed. Some of these include Boceprevir, Telaprevir, and Faldaprevir (NS3/4A protease inhibitors) made for treating Genotype 1. Sofosbuvir (a nucleoside inhibitor of HCV RNA-dependent RNA polymerase) and Velpatasvir (NS5A inhibitor) for treating most all genotypes. Many other direct acting antiviral agents are being tested against other protein/glycoprotein parts of the virus. Patients usually have a liver biopsy before starting treatment, which also establishes the individual's baseline liver status. Only patients who are HCV-RNA positive should be treated (and usually ones with elevated liver function tests). Patients who are active heavy alcohol users, active IV drug users, and patients with decompensated cirrhosis are usually not be treated. Patients with genotype 1 are usually treated for up to 48 months versus 24 months with types 2 through 7. Patients treated with interferon would often rebound (up to 50%) after treatment was completed, but this occurs less with the new direct acting antiviral drugs.

No vaccine is currently available, and many hurdles still exist in its development. The first hurdle in this regard is testing. The only way to test for the potential of infectivity is by PCR for the presence of HCV-RNA. Secondly, the only species that can be infected are humans and chimpanzees, which limit animal testing. The third issue is that many of the HCV viral proteins have a high mutation rate (meaning they are not the same from genotype to genotype). Finally, and possibly the most important, is that researchers currently have not identified an antibody that kills the virus (for example, anti-HBsAg antibody kills the hepatitis B virus). The best hope for a vaccine might be one that prevents the development of the chronic carrier state.

In summary, HCV has rapidly become a difficult and confusing topic with many questions still unanswered. However, the future impact of this virus on society and healthcare is massive. Therefore, further research is needed along with increasing public awareness of this infection. Hopefully, the future will bring an effective immune globulin and vaccine for prevention and research will identify a better mechanism to follow potential infectivity.

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