

Management of Chronic Hepatitis C Virus Infection: Current Perspectives

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Abstract: Worldwide over 300,000 deaths due to liver cancer and cirrhosis occurred in 2013 due to hepatitis C. In the United States about 2% of population has chronic hepatitis C. In 2014 it was the single greatest cause of death in the United States. The number of deaths due to hepatitis C has overtaken HIV/AIDS as a cause of death in USA. Hepatitis C virus (HCV) infection is also prevalent in Africa, Central and East Asia, with highest rates in Egypt. Transmission of HCV in the developed world is intravenous drug use, while in the developing countries the main method of transmission is blood transfusion and unsafe procedures. Once the infecting virions reaches the susceptible cells that are permissive replication. HCV RNA can be detected in blood (including serum and plasma), tears, seminal fluid, ascetic fluid, and cerebrospinal fluid. HCV infection leads to hepatic inflammation, steatosis, cirrhosis, and greater risk of hepatocellular carcinoma. Clinical manifestations include acute infection, chronic infection, non-hepatic complications, and occult infection. Diagnosis including HCV antibody enzyme immunoassay (ELISA), recombinant, and quantitative HCV RNA PCR. Blood tests alleviate the need for liver biopsy. Sofosbuvir with ribavirin and interferon is frequently used drugs. Virus usually (80-90% of cases) recurs in liver transplant patients. Alternative therapies e.g. Milkthistle, ginseng and colloidal gold have no effect on the virus at all. Successful treatment decreases the future risk of hepatocellular carcinoma by 75%. Prevention include screening of blood donors and adhering to universal precautions within the healthcare system.

Keywords: Chronic hepatitis C, Transmission, Management, Prognosis

I. Introduction

Hepatitis C is an infectious disease caused by the hepatitis C virus (HCV) that primarily affects the liver. It is one of five known hepatitis viruses: A, B, C, D, and E [2]. An estimated 130 to 200 million people or 3% of the world's population are living with chronic hepatitis [3]. About 3-4 million people are infected per year, and more than 350,000 people die yearly from hepatitis C related diseases [3]. During 2010 it is estimated that 16,000 people died from acute infections while 196,000 deaths occurred from liver cancer secondary to the infection [4]. It occurs most commonly in Africa and Central and East Asia [5]. About 343,000 deaths due to liver cancer and 358,000 due to cirrhosis occurred in 2013 due to hepatitis C [6]. In the United States, about 2% of people have chronic hepatitis C [7]. The number of deaths from hepatitis C has increased to 15,800 in 2008, having overtaken HIV/AIDS as a cause of death in the USA in 2007 [8,9]. In 2014 it was the single greatest cause of infectious death in the United States [10]. In Europe the percentage of people with chronic infection has been estimated to be between 0.13 and 3.26 [11]. Countries with particularly high rates include Egypt (22%), Pakistan (4.8%) and China 3.2% [3]. Transmission of HCV is primarily by blood-to-blood contact with intravenous drug use, poorly sterilized equipment, needle stick injuries in the healthcare, and transfusion [12]. During the initial infection people have mild or no symptoms. Occasionally a fever, dark urine, abdominal pain, and yellow tinged skin. Virus persists in the liver in about 75% to 85% of those initially infected, and later often leads to liver disease and occasionally cirrhosis [12]. Diagnosis by blood testing for virus antibodies or RNA. Testing is recommended in all people who are at risk [12]. Chronic infection can be cured about 90% of the time with treatments that include the medications sofosbuvir or simeprevir [12]. People with cirrhosis or liver cancer may require liver transplantation, though the virus usually recurs after transplantation [13]. The reviews the current literature on management of hepatitis C virus infections..

II. Discovery of Hepatitis C Virus

When serologic tests for hepatitis A (HAV), and hepatitis B virus (HBV) were developed during the 1970s, it became evident that most cases of transfusion associated hepatitis must be caused by yet another agent, leading to the term non-A, non-B hepatitis (NANB) [14]. In 1987, Michael Houghton and associates at Chiron

Corporation, collaborating with Dr DW Bradley at the Centers for Disease Control and Prevention (CDC), used a novel molecular cloning approach to identify the unknown organism and developed a diagnostic test [15]. In 1988, Alter confirmed the virus by verifying its presence in a panel of NANBH specimens. In April 1989, the discovery of HCV was published in two articles in the journal *Science* [16]. The discovery led to significant improvements in diagnosis and improved antiviral treatment [15]. In 2000, Drs, Alter and Houghton were honored with the Lasker Award for Clinical Medicine Research for “pioneering work leading to discovery of the virus that causes hepatitis C and the development of screening methods that reduced the risk of blood transfusion-associated hepatitis in the U.S. from 30% in 1970 to virtually zero in 2000” [17].

III. Hepatitis C Virus

Hepatitis C virus (HCV) is a small, enveloped, single-stranded, positive-sense RNA virus [13]. It is a member of the *Hepacivirus* genus in the family *Flaviridae* [18,wp,20]. There are seven major genotypes of HCV, which are known as genotypes one to seven [19]. The genotypes are divided into several subtypes with the number of subtypes depending on the genotype. In the United States, about 70 % of cases are by genotype 1, 20% by genotype two and 1% by each other genotypes [7]. Genotype 1 is also the most common in South America and Europe [13]. The half-life of the virus in the serum is around 3 hours and may be as short as 45 minutes [20]. In addition to replicating in the liver the virus can multiply in lymphocytes [21].

HCV and genetic variation

The high level of virus turnover, the absence of proofreading by the NS5B RNA polymerase, and the “tolerance” of many genomic regions for multiple nucleotides results in the relatively rapid accumulation of viral mutations. Multiple HCV variants can be recovered from the plasma and liver of an infected individual at time. As a result, like many RNA viruses, HCV exists in each infected person as a quasi-species, or “swarm” of closely related but distinct genetic sequences [22]. For example, up to 85% of cDNA clones obtained from viral RNAs in the blood of a recently infected individual may present unique genetic variants [23]. During RNA replication, mutations most likely occur in a nearly random fashion throughout the genome, whereas fixation of a substitution within the quasi-species population depends on how that substitution influences viral “fitness” as related to its effect on functional protein/RNA structures, the capacity of the virus for replication, and the host viral interaction [18].

IV. Transmission of HCV

HCV transmission requires that infecting virions contact susceptible cells that are permissive for replication. HCV RNA can be detected in blood (including serum and plasma), saliva, tears, seminal fluid, ascitic fluid and cerebrospinal fluid [24]. HCV-RNA-containing blood is infectious when inoculated intravenously (e.g., by transfusion). In addition a chimpanzee has been infected by intravenous inoculation of saliva [25]. However, there is very little information available regarding the potential infectivity of HCV-RNA containing body fluids. Furthermore, it is not clear whether cells other than hepatocytes can be infected (and thus whether infection requires direct percutaneous inoculation into the blood stream) [18].

The primary route of transmission in the developed world is intravenous drug use (IDU), while in the developing world the main methods are blood transfusion and unsafe medical procedures [26]. The cause of transmission is unknown in 20% of cases [27], however, many of these are believed to be accounted for by IDU [28].

Intravenous drug use

IDU is a major risk factor for hepatitis C in many parts of the world [29]. Of 77 countries reviewed 25 (including the United States) were found to have prevalence of hepatitis C in the intravenous drug user population of between 60% to 80% [29]. Twelve countries had rates greater than 80% [30]. It is believed that ten million intravenous drug users are infected with hepatitis C in China (1.6 million), the United States (1.5 million), and Russia (1.3 million) have the highest absolute totals [30]. Occurrence of hepatitis C among prison inmates in the United States is 10 to 20 times that of the occurrence observed in the general population, this has attributed to high-risk behavior in prisons such as IDU and tattooing with nonsterile equipment [31]. Shared intranasal drug use may also be a risk factor [32].

Nosocomial infection

Blood transfusion, transfusion of blood products, or organ transplants without HCV screening carry significant risks of infection [7]. The United States instituted universal screening in 1992, and Canada instituted universal screening in 1990 [33,34]. This decreased the risk from one in 200 units [33], to between one in 10,000 to 10,000,000 per unit of blood [28]. This low risk remains as there is a period about 11-70 days between the

potential blood donor's acquiring hepatitis C and the blood's testing positive depending on the method[27].Some countries do not screen for hepatitis C due to the cost [35].

Those who have experienced a needle stick injury from someone who was HCV positive have about a 1.8% chance of subsequently contracting the disease themselves[7].The risk is greater if the needle in question is hollow and puncture wound is deep[35].there is risk from mucosal exposures to blood, risk is low, and there is no risk if blood exposure occurs on intact skin[35].Hospital equipment has also been documented as a method of transmission of hepatitis Including reuse of needles and syringes, multiple-use medication vials, infusionbags, and improperly sterilized surgical equipment,among others[35].Limitations in the implementation and enforcement of stringent standard precautions in public and private medical and dental facilities are known to be the primary cause of the spread of HCV in Egypt, the country with highest rate of infection in the world [36].

Sexual transmission

Whether hepatitis C can be transmitted through sexual activity is controversial [37].While there is an association between high-risk sexual activity and hepatitis C and multiple sexual partners are a risk factor for hepatitis C, there is no conclusive evidence that hepatitis C can be transmitted by sexual activity, since people who report transmission with sex as their only risk factor may actually have used drugs but denied[7].The majority of evidence supports there being no risk for heterosexual couples with only one sexual partner[37].Sexual practices that involve higher levels of trauma to the anogenitalmucosa, such as anal penetrative sex or that occur when there is a concurrent sexually transmitted infection including HIV or genital ulceration, do present a risk[37]The United States Department of Veterans Affairs recommend condom use to prevent hepatitis C transmission in those with multiple partners, but not those in relationships that involve only a single partner[38].

Common use items

Personal use-shared items such as razors, toothbrushes, and manicuring or pedicuring equipment can be contaminated with blood. Sharing such items can potentially lead to exposure to HCV[39].Appropriate caution should be taken regarding and medical condition that results in bleeding, such as cuts and sores[40].HVC is not spread through casual contact, such as hugging, kissing or sharing eating or cooking utensils [40].Neither it is transmitted through food or water[41].

Body Tattooing

Tattooing is associated with two to threefold increased risk of hepatitis C[42].This can be due to either improperly sterilized equipment or contamination of the dyes being used[42].Tattoos or piercings performed either before the mid-1980s,"underground" or nonprofessionally are particular concern, since sterile techniques in such settings may be lacking. The risk also appears to be greater for larger tattoos[42].It is estimated that nearly half the prison inmates share unsterilized tattooing equipment[42].It is rare for tattoos in a licensed facility to be directly associated with HCV infection [43].

Maternal transmission

Maternal or mother to child transmission of hepatitis C is less than 10% of pregnancies[44].There no measures that alter this risk[44].It is not clear when transmission occurs during pregnancy, but it may occur both during gestation and delivery[27].A long labor is associated with a greater risk of transmission[35].There is no evidence that breast feeding spreads HCV ,however, to be cautions, an infected mother is advised to avoid breastfeeding if her nipples are cracked and bleeding[45], or if viral loads are high[27].

Transmission Cofactors[18].

Cofactors for HCV transmission chiefly relate to the probability of virus reaching the recipient bloodstream. The donor HCV RNA level matters, especially at the extremes. In a review of 2022 parenteral, sexual, and perinatal HCV exposures, HCV was transmitted only by individuals with detectable viremia [46].Moreover, non-parenteral(e.g., perinatal) transmission of HCV is very rare when the level of viremia is very low[47].Some studies not all studies indicate the infection with HIV may be an important cofactor for both sexual and maternal-infant transmission[48],possibly because HIV infection is also associated with higher HCV RNA levels[49].

V.Pathogenesis

In experimentally infected chimpanzee and in humans HCV RNA can be detected in plasma within days of exposure, often 1 to 4 weeks before liver enzyme levels rise [50].Viremia peaks in the first 8 to 12 weeks of infection, then drops to lower levels and persists[51].In some instances, plasma HCV RNA becomes undetectable in the first few months and remains undetectable indefinitely(viral clearance);in other instances,

viremia is inconsistently detected early and stable pattern of recovery or persistence is not evident for more than six months[51].Some instances of intermittent viremia may reflect reinfection, which has been observed in active injection drug users[52].

Within months of infection, antibodies are detectable in blood to multiple recombinant antigens that correspond to structural and non-structural genes [53].Emergence of HCV-specific antibodies does not correlate temporally with viral recovery.Indeed, although virtually all immunocompetent persons develop antibody responses to someHCV antigens, most infection persist. Viral recovery also has been described in persons with congenital agammaglobulinemia[54].Viral recovery has been associated with a vigorous, blood cellular immune response[55].It appears that in persons with persistent infection,CD4⁺ lymphocyte responses are more difficult to detect in peripheral blood than CD8⁺ lymphocyte responses[56].There is surprisingly little known about why some cellular immune responses are broad and vigorous and others ineffective. Coinfection with HIV or schistosomiasis has been associated with viral persistence, which corresponds with diminished CD4⁺ lymphocyte response [57].

Although HCV infection leads to hepatic inflammation and steatosis the major pathologic consequence of persistence HCV infection is the development of hepatic fibrosis, which may progress to life threatening cirrhosis and greatly risk of hepatocellular carcinoma. These long- term complications generally occur more than 20 years after the onset of infection, though more rapid progression has been reported [58].

VI. Clinical Manifestations

Acute infection

Hepatitis C infection causes acute symptoms in 15 % of cases[59].Symptoms are generally mild and vague, including a decreased appetite, fatigue ,nausea, muscle or joint pain, and weight loss[7],and rarely acute liver failure result[60].Most cases of acute infection is not associated with jaundice[61].The infection can be resolved spontaneously in 10-50% of cases, which occurs more frequently in individuals who are young and female[61].HCV RNA can be detected in blood within days of exposure and is followed by elevations in serum levels of liver specific enzyme and alanine aminotransferase(ALT),aspartate aminotransferase(AST) and in some cases bilirubin [62].

Chronic infection

About 80 % of those exposed to the virus develop chronic infection [30].This is defined as the presence of detectable viral replication for at least for six months. Most experience minimal or no symptoms during the initial few decades of the infection [63].Chronic hepatitis may be associated with fatigue[18],and mild cognitive problem [64].Chronic infection after several years may cause cirrhosis or liver cancer[13].The liver enzymes are normal in 7- 53%.The late relapses after apparent cure have been reported but these can be difficult to distinguish from reinfection[65].

Fatty changes to the liver occur in about half of those infected and are usually present before cirrhosis develops [66].Usually (80% of the time) this change affects less than a third of the liver[66].Worldwide hepatitis C is the cause of 27% of cirrhosis cases and 25 % hepatocellular carcinoma[35].About 10 to 30% of those infected develop cirrhosis over 30 years[13,7]..Cirrhosis is more common in those also infected with hepatitis B, Schistosoma, orHIV,inalcoholics and those of male gender[7].In those with hepatitis C,excess alcohol increases the risk of developing cirrhosis 100 fold[67].Those who develop cirrhosis have a 20 fold greater risk of hepatocellular carcinoma. This transformation occurs at a rate of 1-3% per year [13,7].Being infected with hepatitis B in addition to hepatitis C increases this risk further[68].Liver cirrhosis may lead to portal hypertension, ascites(accumulation of fluid in the abdomen) easy bruising or bleeding, varicose (enlarged veins, especially in the stomach and esophagus),jaundice, and a syndrome of cognitive impairment known as encephalopathy[69].Ascites occurs at some stage in more than half of those who have chronic infection[70].

Non-hepatic complications

The common problem due to hepatitis C but not involving the liver is mixed cryoglobulinemia (usually the type 11 form)-an inflammation of small and medium-sized blood vessels [71].Hepatitis C is also associated with autoimmune disorder Sjogrens syndrome,a low platelet count, lichen planus porphyria cutanea tarda,neurolytic acral erythema, insulin resistance, diabetes mellitus, diabetic nephropathy, autoimmune thyroiditis,and B-cell lymphoproliferative disorders[72],20-30% of people infected have rheumatoid factor-a type of antibody [73].Possible association include Hyde's prurigonodularis [74],and membranoproliferative glomerulonephritis[65].Cardiomyopathy with associated with abnormal heart rhythms has also been reported[75].A variety of central nervous system disorders has been reported. Chronic infection seems to be associated with an increased risk of pancreatic cancer [76,77].

HCV negative or occult infection

Persons who have been infected with hepatitis C may appear to clear the virus but remain infected. The virus is not detectable with conventional testing but can be found with ultra-sensitive tests[78,79].The virus can be detected by antibody test for virus core protein and the viral genome[80].It may be found in people with anti-hepatitis C-antibodies but with normal levels of liver enzymes 'in antibody- negative people with ongoing elevated liver enzymes of unknown cause, in healthy populations without evidence of liver disease, and groups at risk for HCV infection including those on hemodialysis or family members of people with occult HCV.The clinical relevance of this form of infection is under investigation [81].The rate of occult infection in those apparently cured is controversial but appears to be low[66].

HCV in children and pregnancy

Worldwide the prevalence of hepatitis C virus infection in pregnant women and children has been estimated to 1-8% and 0.05-5% respectively [84].Vertical transmission has been estimated to be 3-5% and there is a high rate of spontaneous clearance(25-50%) in the children. Higher rates have been reported for both vertical transmission(18%,6-36%) and 41%)[83],and prevalence in children(15%)[84].Factors associated with an increased rate of infection include membrane rupture of longer than 6 hours before delivery and procedures exposing the infant to maternal blood[85]. Higher HCV infection has been reported in immunocompromised and those with human immunodeficiency virus infection, recipients of organ transplants, and those with hypogammaglobulinemia. Infection in these people is associated with an unusually rapid progression to cirrhosis [86].

VII. Diagnosis

There are variety of diagnostic tests for hepatitis, including HCV antibody enzyme immunoassay or ELISA, recombinant, and quantitative HCV RNA polymerase chain reaction (PCR)[7]HCV RNA can be detected by PCR typically one to two weeks after infection, while antibodies can take substantially longer to form and thus be detected[69].Chronic hepatitis C is defined as infection with the hepatitis virus persisting for more than six months based on the presence of its RNA[63].Chronic infections are typically asymptomatic during first few decades, and thus are most commonly discovered following the investigation of elevated liver enzymes levels or during screening of high risk individuals. Testing is not able to distinguish between acute and chronic infections [63,35].Diagnosis in the infant is difficult as maternal antibodies may persist for up to 18 months[87].

Serological tests

Hepatitis C testing typically begins with blood testing to detect the presence of antibodies to the HCV, using an enzyme immunoassay[7]If test is positive, a confirmatory test is then performed to verify the immunoassay and to determine the viral load[7].A recombinant immunoblot assay is used to verify the immunoassay and the viral load is determined by an HCV RNA polymerase chain reaction[7].If there is no RNA and the immunoblot is positive, it means that person tested had previous infection but cleared it either with treatment or spontaneously; if the immunoblot is negative, it means that immunoassay was wrong[7].It takes about 6-8 weeks following infection before the immunoassay will test positive[18].Liver enzymes are variable during initial part of infection[63],and on average begin to rise at seven weeks after infection[18].The elevation of liver enzymes does not closely follow disease severity[18].

Biopsy and Screening

Liver biopsies are used to determine the degree of liver damage present, however, there are risks from the procedure[13].The typical changes seen are lymphocytes within the parenchyma, lymphoid follicles in portal triad, and changes to the bile ducts[13].There are number of blood tests available that try to determine the degree of hepatic fibrosis and alleviate the need for biopsy[13].Screening for HCV is recommended for those at high risk, which includes injecting drug users, those who have received blood transfusion before 1992[88],those have been in jail, those on long term hemodialysis[89],and those with tattoos[42].Screening also recommended in those with elevated liver enzymes, as this frequently the only sign of chronic hepatitis[90].Routine screening is not recommended in the united States[7].

VIII. Management

HCV induces chronic infection in 50-80% of infected persons.Approximately 40-80% of these clear with treatment[91].In rare cases infection can clear without treatment[28].Those with chronic hepatitis C are advised to avoid alcohol and medications toxic to liver[7].Ultrasound surveillance for hepatocellular carcinoma is recommended in those with accompanying cirrhosis[7].Treatment with antiviral medication is recommended in all people with proven chronic hepatitis C who are not risk of dying from other causes[92].People with highest complication risk should be treated first, with the risk of complications based on the degree of liver

scarring[92]The initial recommended treatment depends on the type of hepatitis C virus with which a person is infected[92],e.g.,treatment for HCV genotype 1a,HCV genotype 1b,HCV genotype 2,HCV genotype 3,HCV genotype 4, and HCV genotype 5 or 6 is different[92].

Sofosbuvir with ribavirin and interferon appears to be around 90% effective in those genotype 1,4,5 or 6 disease[93].Sofosbuvir with just ribavirin appears to be 70 to 95% effective in type 2 and 3 disease but has higher rates of adverse effects[93].Treatment during the first six months is more effective than once hepatitis C has become chronic[69].

Surgical intervention

Cirrhosis due to hepatitis C is a common reason for liver transplantation[69],though the virus usually (80-90% of cases) recurs afterwards[15].Infection of the graft leads to 10-30% of people developing cirrhosis within five years[94].Treatment with Pegylated interferon and ribavirin post-transplant decreases the risk of recurrence to 70%[95].

Several alternative therapies are claimed by their proponents to be helpful for hepatitis C including milk thistle,ginseng,and colloidal silver[96].However no alternative therapy has shown to improve outcomes in hepatitis C,and no evidence exists that alternative therapies have any effect on the virus at all[96].

XI. Prognosis And Prevention

The responses to treatment is measured by sustained viral response(SVR),defined as the absence of detectable RNA of the hepatitis C virus in blood serum for at least 24 weeks after discontinuing the treatment[97],and rapid virological response (RVR) defined as undetectable levels achieved within four weeks of treatment. Successful treatment decreases the future risk of hepatocellular carcinoma by 75% [98]. Prior to 2012 sustained response occurs in about 40-50% in people with HCV genotype 1 given 48 weeks of treatment[13].A sustained response is seen in 70-80% of people with HCV genotypes 2 and 3 with 24 weeks of treatment[13].A sustained response occurs about 65% in those with genotype 4 after 48 weeks of treatment. The evidence for treatment in genotype 6 diseases is sparse and what evidence there is support 48 weeks of treatment at the same doses used for genotype 1 disease [99]

Prevention

As of 2016,no approved vaccine protects against contracting hepatitis C[100].However, there are a number of vaccines under development and some shown encouraging results[99].A combination of harm reduction strategies, such as the provision of new needles and syringes and treatment of substance use, decreases the risk of hepatitis C in intravenous drug users by about 75%[101].Screening of blood donors is important at a national level, as adhering to universal precautions within healthcare facilities[18].In countries where there is an insufficient supply of sterile syringes, medications should be given orally rather than via injection-when possible[35].

IX. Conclusion

Hepatitis C related diseases have high mortality worldwide. Disease is more common in Africa and Central and East Asia. Countries with high rates include Egypt, Pakistan and China.High number of deaths due to liver cirrhosis and liver cancer. Diagnosis by blood tests for virus antibodies or RNA.Treatment with antiviral drugs. There is number of vaccines under development.

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