

# Hepatitis C

## *An update*

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### ABSTRACT

Hepatitis C is a long-term viral infection affecting the liver caused by the hepatitis C virus (HCV). Hepatitis C can be silent for years before symptoms appear, and liver damage occurs. The hepatitis C virus is extremely infectious, which means that only a tiny amount of HCV can cause illness. Hepatitis C is a major public health problem worldwide with far-reaching implications because of the chronicity of the infection that leads to chronic liver disease, cirrhosis, and primary hepatocellular carcinoma.

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**H**epatitis C is an inflammation of the liver caused by the hepatitis C virus (HCV). The virus is a ribonucleic acid (RNA) virus classified as a flavivirus, a member of the family of Flaviviridae. The virus is mainly an hepatotropic virus although its replication occurs also extrahepatically. Patients who suffer from acute hepatitis C may experience no symptoms or, in approximately 30-40% of cases, develop illness lasting for few days or weeks with symptoms generally quite mild and non-specific (flu like). Usually liver blood tests are not measured and hepatitis C is not suspected or diagnosed. Infection may first become apparent only on the development of liver failure or liver cancer several decades after initial infection. The HCV mutates rapidly and, because of this rapid mutation, the immune system typically cannot eradicate the virus,

and so it remains in the body of most infected people. The major characteristic of HCV is the tendency to cause chronic liver disease. At least 75% of patients with acute hepatitis C ultimately develop chronic infection, and most of these patients have accompanying chronic liver disease. Approximately 25% of patients acutely infected with hepatitis C go on to clear the infection as evident by normalization of aminotransferase levels and undetectable serum HCV RNA. The HCV accounts for approximately 15% of acute viral hepatitis, 60-70% of chronic hepatitis, and up to 50% cirrhosis, end-stage liver disease, and hepatocellular carcinoma (HCC). Certain factors may increase the progression to chronicity in a patient who is acutely infected with HCV. Older patients and patients with a shorter time between infection and diagnosis, male-gender, HBV, or HIV co-infection, or both, genotype, and mode of transmission have all been associated with rapid disease progression.<sup>1,2</sup>

**Hepatitis C virus structure.** After the isolation of HCV, and the identification by molecular cloning of the virus genome in 1989, it became the target of intensive research by several investigators.<sup>3</sup> Now it is well known that HCV is a spherical enveloped virus 30-50 nm in diameter with an outer envelope, which consists of a lipid and 2 glycoproteins, E1 and E2. The surface protein, E2, inhibits the immune system's activity against the virus. The core genome, consisting of linear single stranded RNA of 9400 nucleotides, belongs to the genus of Flavivirus. The genomic RNA encodes a large viral polypeptide of approximately 3000 amino acids, this large polypeptide is proteolytically processed by cellular peptidases and viral proteases into structural and non-structural proteins.<sup>4</sup> The structural proteins, include the capsid or core protein C, 2 envelope proteins E1 and E2, and a small protein of unknown function P7. All structural proteins are located in the N-terminal third. The non-structural proteins, named NS2, NS3, NS4A, NS4B, NS5A, and NS5B, are necessary for viral replication.<sup>5-7</sup> The HCV has one serotype and multiple

genotypes. The HCV classification into genotypes is based on sequence differences in the viral genome, corresponding to the main branches in the phylogenetic tree, and into subtypes corresponding to the more closely related sequences within some genotypes.<sup>5</sup> At least 6 major genotypes, and more than 80 subtypes are described. The major genotypes have been numbered 1 to 6, and the subtypes a, b and c.<sup>8</sup> All genotypes have been found to be hepatotropic and pathogenic. There is no association between genotype and mode of acquisition of infection. Some genotypes of HCV appear to be geographically restricted, while others have worldwide distribution.<sup>8,9</sup> In the United States, genotype 1 is most prevalent (approximately 75%), while genotypes 2 (10.8%), 3 (5.8%) and 4 (1.7%) are less common. The HCV type 1b is the most prevalent subtype in most parts of Asia and Japan. In European types, 1b and 2 are widely distributed, particularly in older age. Knowledge of the genotype of HCV is helpful in defining the epidemiology of hepatitis C. Once the genotype is identified, it needs not be tested again; genotypes do not change during the course of infection. Prior infection does not protect against reinfection with different genotypes of the virus. For this reason, there is no effective pre- or post-exposure prophylaxis (namely, immune globulin). There seems to be a correlation between HCV genotype and response to antiviral therapy. Patients infected with genotype 1 and genotype 4 respond poorly to interferon treatment compared with patients infected with genotypes 2 and 3. The HCV subtype 1b has been considered to be associated with poorer response to interferon treatment, more rapid disease progression, and a greater rate of development of HCC than other HCV subtypes.<sup>10</sup>

**Epidemiology.** The prevalence rate of HCV worldwide is primarily related to socioeconomic status and so varies markedly. According to the World Health Organization, 170-200 million people globally are chronically infected with HCV, which means that approximately 3% of the world population is at risk of developing serious complications.<sup>11-14</sup> In the United States, where 1.8% of the population is infected with HCV, there are 3.9 millions HCV carriers and 36,000 new cases of acute hepatitis C annually (**Table 1**). In Canada, an estimated 250,000 people are HCV positive. In Mediterranean Europe the prevalence of HCV is 1.05%, in Asia 2.15% and in Africa 5.3%. China is estimated to account for one fourth of chronic HCV infections worldwide. In Egypt and in areas of Japan and Taiwan, HCV prevalence may be as high as 10-30%, mostly in adults above 40 years of age.<sup>14</sup> Persons infected with HCV serve as a source of transmission to others and are at risk for chronic liver disease, or other HCV-related chronic diseases, during the first 2

or more decades following initial infection. Within 3-6 weeks of infection with the HCV, the production of anti-HCV antibodies begins. Although our antibodies fight the virus, only approximately 15% of patients acutely infected with HCV lose virologic markers for HCV and are cured. However, in 80-85% of cases the virus is not eliminated and, following the acute phase of infection, they are left with a long-term chronic HCV infection. Female sex and young age are independently associated with a more favorable outcome of acute hepatitis C.<sup>15</sup> Chronic HCV infection is more common in males (2.5%) than in females (1.2%), and in those who acquired the infection when aged above 40 years and in patients who drink heavily.<sup>2,16</sup> Chronic hepatitis C infection is responsible for approximately 8,000 to 10,000 annual deaths from cirrhosis and HCC, which are the major complications of chronic HCV infection. Chronic hepatitis C is the most common cause of cirrhosis and HCC in the United States.<sup>17</sup> Of long-term chronic HCV infections, 10-20% will develop cirrhosis and individuals with cirrhosis from hepatitis C are also at an increased risk of developing HCC (1-5%). The time from HCV transmission to the development of cancer ranges from 10-50 years with a median of 30 years. More than half of newly diagnosed cases of chronic liver disease are due to hepatitis C and between 30-40% of liver transplants carried out in adults is due to hepatitis C.<sup>18</sup> The factors which influence in early development of cirrhosis and cancer in HCV patients are: alcohol, smoking, liver toxic drugs, exposure to chemicals, stressful life style, hepatitis B co-infection, hereditary tendency to cirrhosis, or cancer. Repeated inflammation, necrosis, and regeneration in the liver over a long period may trigger carcinogenesis.<sup>19</sup> Genotype 1b, large inocula of HCV (as in post-transfusion hepatitis C), and poor host immune response are all independent risk factors associated with an increased chance of developing chronic hepatitis C.<sup>20</sup> In patients with HCV associated cirrhosis, the incidence of HCC is 4 times higher in comparison with cirrhosis of other etiologies.<sup>21</sup>

**Risk factors for HCV.** Transfusion of infected blood or blood products, use of contaminated dialysis equipment, transplantation of infected organs, sharing

**Table 1** - Prevalence of hepatitis C virus (HCV) infection in the USA.

Parameters	Percentage
Drug users <5 years	85
Intra-familial history of liver disease	2
Transfusions of blood	1
Babies born from HCV positive mothers	5
Healthcare workers	1.3

of contaminated needles among injection drug users, and occupational injury with needle blood contamination are well-recognized modes of HCV transmission. However, almost 40% of patients do not have a history of parenteral exposure. Perinatal exposure is associated with HCV infection, but HCV transmission by this route is low. The average rate of HCV infection among infants born to HCV-positive mothers is approximately 5-6% based on detection of anti-HCV and HCV RNA.<sup>22-24</sup> The HCV transmission to infants occurs at the time of birth, and there is no treatment that can prevent this from happening. The risk of maternal-infant spread rises with the amount of virus in the mother's blood. Data regarding the relationship between delivery mode and HCV transmission are limited and presently indicate no difference in infection rates between infants delivered vaginally compared with cesarean-delivered infants. The transmission of HCV infection through breast milk has not been documented. Close contact such as sexual behavior and kissing, sharing toothbrushes and razors may be involved in the intrafamilial spread of hepatitis C even with a low prevalence.<sup>25</sup> The prevalence of specific risk factors in persons with HCV infection has changed over the past 10 years. The incidence of transfusion-associated hepatitis (TAH) was 8-10 per 100 persons transfused prior to 1985. With the introduction of first generation anti-HCV tests in the early 1990's, the rate of HCV acquisition via blood products declined and current estimates that the incidence of TAH is less than 1%.<sup>26</sup> Similarly, patients with hematological disorders requiring blood products, such as clotting factors and immune globulin, from pooled donors had a nearly 100% rate of HCV-positivity. However, changes in product manufacturing factors with effective inactivation procedures, as well as the use of screening assays, have significantly reduced the incidence of HCV transmission in this population. Hemodialysis patients are at high risk of infection by HCV. The prevalence of HCV antibodies among hemodialysis patients ranges from 2% in northwestern Europe to 76.3% in Indonesia.<sup>27,28</sup> Dialysis specific risk factors associated with anti-HCV positivity include a history of prior blood transfusion, volume of blood transfused, and partial immunosuppression. The duration of hemodialysis treatment and the possibility of nosocomial HCV transmission has also been suggested as additional contributing elements.<sup>28</sup> Partial immunosuppression in these patients, resulting in a poor antibody response, may be a contributing factor. Although hemodialysis patients constitute a risk group for HCV acquisition, they account for only 1% of persons with chronic infection. The prevalence of HCV infection among drug users in the United States varies from 72-89%.<sup>29</sup> The factor most consistently associated with anti-HCV positivity

is duration of drug use, with anti-HCV positivity rates of 54% among users of less than a year, 78% among users of one year, 83% among users of 5 years, and 94% among users of more than 10 years.<sup>30</sup> Intravenous drug users account for approximately two thirds of all cases of hepatitis C. Among newly diagnosed cases of chronic liver disease secondary to HCV in 1998, up to 60% report an antecedent history of intravenous drug use. The prevalence of other risk factors (for example, occupational) has remained constant over time. Health care workers who suffer needle-stick accidents account for approximately 4% of new infections. The seroprevalence of anti-HCV among healthcare workers in the United States ranges from 0.7-2%.<sup>29</sup>

**Diagnostic tests.** Two categories of virologic assays are used for the diagnosis and management of HCV infection: serologic assays based on HCV immunologic characteristics, namely, specific antibodies produced by immune cells in response to viral antigenic stimulation, and molecular assays based on the quantification and characterization of the HCV RNA.<sup>31-33</sup> The US Food and Drug Administration (FDA) has approved for diagnosis of HCV infection, those tests that detect the presence of antibodies to HCV. Anti-HCV antibodies can be found from 3-6 weeks after infection with the virus, and within months after symptoms begin. The ELISA test for the HCV antibody is an important diagnostic test that detects the HCV antibodies in approximately 70-90% of infected patients. The presence of anti-HCV antibodies indicates exposure to the infection but does not distinguish between acute, chronic, or resolved infection. In patients with spontaneously resolving infection, anti-HCV antibodies may persist throughout life, fall slightly while remaining detectable, or gradually disappear after several years, although they may become undetectable in hemodialysis patients or in cases of profound immunodepression. Anti-HCV antibodies always persist for life in patients who develop chronic infection. The Recombinant Immunoblot Assay (RIBA), which are more specific and sensitive than ELISA, are particularly useful for confirmation of HCV infection. The utility of RIBA testing is to decrease false positive ELISA tests that may still be seen in individuals with no apparent risk factors for HCV, and those with other immune-mediated disease, for example, rheumatoid arthritis.<sup>34,35</sup> Unlike antibody tests, HCV RNA tests directly measure the presence of the HCV. The polymerase chain reaction (PCR) test came onto the market in late 1994. Testing for HCV RNA by PCR confirms the diagnosis and documents that viremia is present. The HCV RNA tests may be qualitative or quantitative. Qualitative HCV RNA tests are used to diagnose hepatitis. Quantitative HCV RNA tests determine the viral load. The HCV RNA

levels are stable over time in patients with chronic infection. The HCV RNA level may increase slightly after several years of chronic infection. The HCV RNA can be detected in serum or plasma within 1-2 weeks after exposure to the virus and weeks before the onset of alanine-aminotransferase (ALT) elevations or the appearance of anti-HCV antibodies. Detection of HCV RNA might be the only evidence of HCV infection in immunocompromised patients, for example, patients on hemodialysis, and in patients in the early course of HCV infection before HCV antibodies develop.<sup>28</sup> In acute hepatitis C, the increase in ALT and aspartate aminotransferase (AST) is greater than 10-fold in elevation, while in chronic hepatitis C the elevation is usually less than 5 times the upper limit of normal.

**Clinical course.** The incubation period of hepatitis C infection averages 6-7 weeks, with a range of 2 weeks to 6 months. Persons with acute HCV infection are either asymptomatic or have a mild clinical illness. Clinical illness in patients with acute hepatitis C who seek medical care is similar to other types of viral hepatitis, and serologic testing is necessary to determine the etiology of hepatitis in an individual patient. In patients with clinical illness, the onset is usually insidious with anorexia, low-grade fever, abdominal discomfort, nausea, and vomiting, muscle and joint pains, malaise and fatigue progressing to jaundice. Patients with chronic hepatitis C have few, if any, symptoms. The most common symptom is intermittent fatigue. In some patients, right upper quadrant pain in the liver, nausea, and poor appetite occur. The major long-term complications of chronic hepatitis C are cirrhosis, end-stage liver disease, and HCC. Once cirrhosis is present, the ultimate prognosis is poor. Occasionally extra-hepatic manifestations of chronic HCV infection occur. Extra-hepatic manifestation of immunologic origin is the essential mixed cryoglobulinemia, in which HCV may form immune complexes with anti-HCV. The deposition of immune complexes may cause small-vessel damage. Complications of cryoglobulinemia include rash, vasculitis, and glomerulonephritis. Other extra-hepatic complications of HCV infection include focal lymphocytic sialadenitis, autoimmune thyroiditis, porphyria cutanea tarda, lichen planus, Mooren corneal ulcer, idiopathic pulmonary fibrosis, polyarteritis nodosa, aplastic anemia, and B-cell lymphomas. Rarely myocarditis as an extra-hepatic manifestation of HCV infection may occur. The exact mechanism of myocytes injury by HCV is still unclear, but clinical studies support that an immune-mediated mechanism may play a more major role than a direct viral cytotoxic effect of HCV on the myocardium.<sup>36</sup>

**Therapy.** Until recently the best treatment for HCV was considered to be monotherapy with interferon,

an antiviral drug that inhibits the viral replication. The administration of interferon for HCV patients was success in only approximately 10-20% of the cases.<sup>37</sup> In 1998, the Food and Drug Administration (FDA) approved the combination treatment of alfa2b-interferon, 3 million units 3 times weekly, plus ribavirin, 1.000-1.200 mg daily in chronic HCV patients for 6-12 months. This therapy is not entirely successful. Factors associated with favorable response to therapy are low pretreatment serum HCV RNA level, HCV genotypes 2 and 3, and absence of cirrhosis or significant fibrosis in liver biopsy.<sup>38</sup> The HCV genotypes 2 and 3 have been shown to have higher, 80%, sustained response rate than 50% of genotype 1.<sup>20,39</sup> A sustained response is where no presence of HCV RNA can be detected immediately after therapy and for 6 months afterwards. Recent reports concerning combination therapy with IFN and ribavirin show that complete clearance of viremia is observed for at least 4 years. Since many patients who initially respond to treatment later experience viral rebound, sustained virologic response rates are invariably lower than response rates reported in the middle and at the end of therapy. Investigators have reported that responders have a more rapid fall in serum HCV RNA level during the first few weeks of treatment.<sup>38</sup> Interferon monotherapy is generally reserved for patients in whom ribavirin is contraindicated, such as those with anemia, heart disease, stroke, kidney disease, and pregnant woman. Ribavirin, when used alone, does not work. Combination therapy using interferon and ribavirin is now FDA approved for the use in children aged 3-17 years. Today the treatment of choice for chronic hepatitis C is peginterferon, commonly called pegylated, which lasts longer in the body, is twice as effective as regular interferon and can be injected once rather than 3 times weekly, plus daily ribavirin. Interferon therapy is expensive due to the high cost of recombinant human interferons, the large doses and lengthy course of administration necessary to achieve maximum response rates in recipients. Side effects, usually reversible, from this type of HCV treatment include severe flu-like symptoms, anorexia, extreme fatigue, anxiety, hair loss, autoimmune disease, diabetes mellitus hyper or hypothyroidism nephropathy, leukopenia, thrombocytopenia, mental confusion, and depression. A small percentage of patients may experience severe psychological side effects, with or without pre-existing psychiatric disorders, such as psychosis or suicidal behavior. These mentioned adverse reactions are dose-dependent and reverse rapidly when therapy is stopped.<sup>40</sup> Despite impressive progress in the management of chronic hepatitis C over the past 10 years, treatment failure still occurs in a great number of patients, and so the search for new treatments is

ongoing. Such treatments include the HCV protease inhibitors. Although protease inhibitors are not yet clinically available, they represent the most promising drugs for targeting HCV. These drugs specifically target HCV by attempting to block the HCV serine protease, enzyme that plays a crucial role in viral replication.<sup>41</sup>

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