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# Overview

Infection with hepatitis C virus (HCV) is the commonest bloodborne infection in the United States. Most persons with HCV infection have persistent (rather than acute) infection; these persons usually remain asymptomatic for many years and most do not become aware of their infection until they develop chronic hepatitis and are tested for anti-HCV antibodies. The U.S. Centers for Disease Control and Prevention (CDC) estimates that 40% of patients with chronic liver disease have HCV-related illness. Transmission of HCV in the United States was most intense prior to the 1990s – large numbers of persons who acquired infection in the 1960s, 1970s, and 1980s are expected to have complications from HCV infection during the coming years and the number of deaths from chronic liver disease could substantially increase.

HCV transmission is primarily caused by direct, percutaneous exposure to infected blood. Prior to 1990, when a serologic test for HCV infection first became available, most cases resulted from receiving a blood transfusion. The majority of transfusion-related non-A, non-B hepatitis cases that occurred before 1994 are now known to have been caused by HCV. After 1994, CDC has not been able to detect any risk of HCV infection from blood transfusions. Injecting-drug use now accounts for the majority of new cases of HCV transmission in the United States.

This report presents information about HCV. Included are discussions of the clinical features, epidemiology and transmission, molecular biology, diagnosis, and preventive measures. Treatment of HCV infection is rapidly evolving and is not covered. References to authoritative and helpful resources are included.

## Acknowledgements -----

Geronimo Sahagun, M.D. and Brian McMahon, M.D. provided Alaska specific information about HCV infection.

# Clinical features and natural history-----

**Incubation period** - The incubation period for acute infection is measured by the time from percutaneous exposure to HCV until the serum alanine aminotransferase (ALT) level becomes elevated. Although HCV RNA can be detected in the blood within 1-3 weeks after exposure, the onset of acute symptoms averages 6-7 weeks (50 days).<sup>1</sup> Many patients have mild or unrecognized acute symptoms.

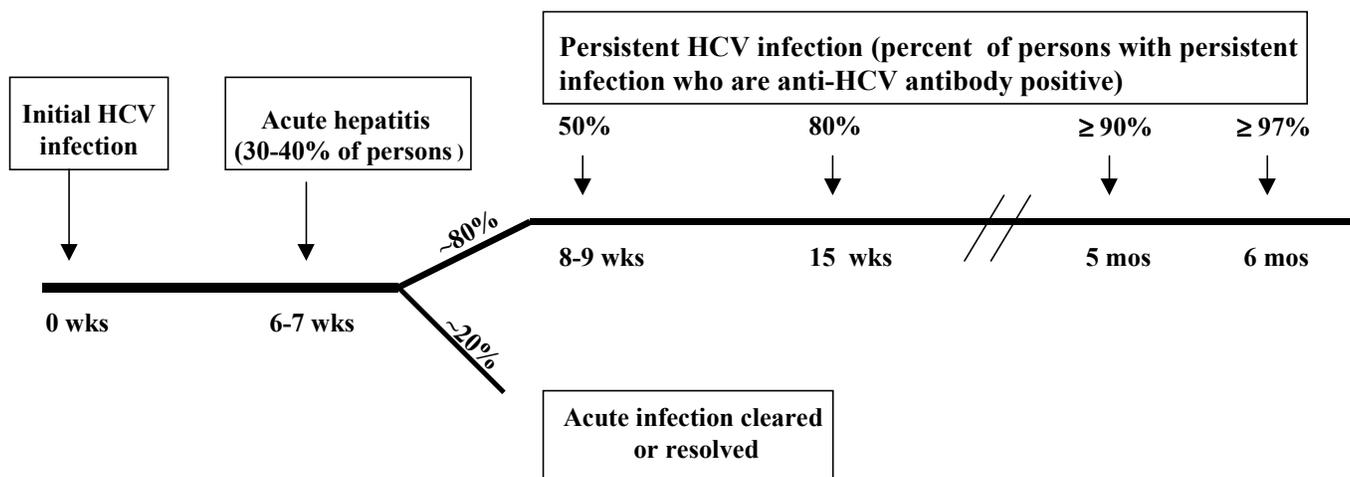
**Acute infection** - The majority of persons with acute HCV infection are asymptomatic; 30% to 40% develop jaundice, malaise, abdominal pain, or anorexia.<sup>1</sup> HCV cannot be differentiated from other causes of hepatitis without laboratory testing. Fulminant hepatic failure after acute non-A, non-B hepatitis or HCV infection has been reported but is rare.<sup>1</sup>

Following acute HCV infection, about 80% of persons develop persistent infection. Only about 20% of acute infections are “cleared” or

resolved. Persons with resolved infection have no evidence of HCV RNA in their blood, normal serum ALT levels, and may or may not have antibodies to HCV (anti-HCV antibody). Among a small group of patients who cleared HCV infection following posttransfusion hepatitis caused by HCV infection, 53% became anti-HCV antibody negative within 1 to 9 years.<sup>2</sup>

**Persistent infection** - Following acute infection, about 80% of persons develop persistent HCV infection.<sup>1</sup> Almost all persons with persistent infection eventually develop anti-HCV antibody and have HCV RNA detectable in their blood. Anti-HCV antibody becomes detectable in approximately 80% of persons within 15 weeks after the onset of persistent infection. Five months after infection, 90% or more have anti-HCV antibody, and 6 months after infection, more than 97% have detectable anti-HCV antibody (Figure 1).

**Figure 1. Incubation period and proportion of persons with positive anti-HCV antibody test**



A variety of ALT patterns have been observed in patients with histologically confirmed persistent HCV infection. Serum ALT levels may return to normal, suggesting recovery; however, subsequent ALT elevations are not unusual, indicating persistent HCV infection and chronic hepatitis.<sup>3</sup> Up to one-third of patients may have prolonged periods (12 or more months) of normal ALT activity.<sup>1,3</sup>

Overall, approximately 65% of persons with persistent HCV infection eventually develop chronic hepatitis manifested as periodic or continuous ALT elevations.<sup>4</sup> Persistent HCV infection generally progresses slowly with few symptoms for decades after acute infection. Approximately 20% of persons develop nonspecific symptoms such as mild fatigue and malaise; however, many persons do not have any symptoms until they have advanced liver disease.<sup>1</sup>

Cirrhosis develops in 10% to 20% of patients with chronic hepatitis within 2 to 3 decades after infection.<sup>3</sup> The risk of developing severe liver disease is difficult to measure because only a small number of studies have followed patients from the onset of infection. Estimates of the risk of developing cirrhosis vary widely, from 2% to 50% of patients with persistent HCV infection.<sup>5</sup> Potential risk factors predicting cirrhosis among persons with persistent HCV infection have not been clearly defined.<sup>6</sup> Several studies have found an association between infection with HCV genotype 1b and more severe chronic hepatitis and cirrhosis; however, other studies have not seen this association.<sup>3</sup> Increased risk of complications is associated with male gender, age over 40 years at the time of initial infection, and immune deficiency.<sup>3,5</sup>

Alcohol intake is strongly correlated with severe infection and fibrosis, and is associated with the rapid development of cirrhosis or end-stage liver

disease.<sup>1,3</sup> A large number of patients with alcoholic cirrhoses have HCV infection, and some studies have shown higher levels of serum HCV RNA with even moderate alcohol consumption.<sup>6,7</sup>

After cirrhosis is established, patients with persistent HCV infection are at risk for developing portal hypertension, hepatocellular failure, and hepatocellular carcinoma. Case-control studies excluding other factors (e.g., alcoholic liver disease or HBV infection) have found that anti-HCV antibody positive persons have a 5- to 7-fold higher risk of developing hepatocellular carcinoma than anti-HCV antibody negative persons.<sup>8</sup> Hepatocellular carcinoma is believed to occur more frequently because of the long-term inflammation and regeneration associated with chronic hepatitis.<sup>1</sup> The risk of developing hepatocellular carcinoma in persons with persistent HCV infection appears to be 1% to 5% after 20 years, with an average interval of 30 years (range: 15-60 years) after infection.<sup>1,3,5</sup> After developing cirrhosis, the risk of hepatocellular carcinoma is estimated to increase to 1% to 4% per year.<sup>1,5</sup>

***Extrahepatic manifestations*** - Persistent HCV infection has been associated with extrahepatic autoimmune disorders. An essential mixed cryoglobulinemia develops in about 1% to 2% of patients, although cryoglobulins may be detected in the serum of about one-third of persons with HCV infection.<sup>1</sup> Other extrahepatic immune manifestations in patients with persistent infection include arthritis, thyroid disorders, Sjögren's syndrome, keratoconjunctivitis sicca, lichen planus, and glomerulonephritis.<sup>1,6,9</sup> Persistent HCV infection may be an underlying cause of porphyria cutanea tarda.<sup>1</sup> Reports of patients with porphyria cutanea tarda suggest that 20% of such patients in the United States, and 60% or more of patients in southern Europe, are anti-HCV antibody positive.<sup>5,9</sup>

**Mortality** - The long-term mortality of persistent HCV infection has not yet been determined. In a study examining mortality rates among patients with acute non-A, non-B hepatitis, 67% of which were anti-HCV antibody positive, hepatitis patients were matched with controls who had received transfusions but did not develop non-A, non-B hepatitis. After an average follow-up of 18 years, there was no difference in overall mortality between the two groups. Although liver related mortality was rare, it occurred more frequently in hepatitis patients (3.2%) than in controls (1.5%).<sup>10</sup>

Other studies of patients with posttransfusion HCV infection found mortality rates for liver disease varying from 3% to 5% over 16-23 years of follow-up. In a cohort of an estimated 2,000 to 6,400 women in Ireland who received HCV-contaminated Rh immune globulin and in which 390 cases of persistent HCV infection were subsequently confirmed, there was no evidence after 14 years of follow-up of increased liver-related mortality among the women with persistent HCV infection.<sup>11</sup>

A study in the United Kingdom examined mortality due to liver disease and liver cancer among men with hemophilia who had been treated with blood products before 1986. Although the study population could not be formally classified by HCV status, other studies of similar groups have found HCV infection rates as high as 90%. For men not infected with HIV (human immunodeficiency virus), the cumulative death rate due to liver disease or liver cancer was 1.4%; rates ranged from 0.1% for men first exposed to blood products before 25 years of age to 14.3% for those first exposed after age 45. For men co-infected with HIV, the mortality rate for liver disease or liver cancer was 6.5%; rates ranged from 3.8% for those first exposed before age 25 years to 18.7% for those exposed after 45 years of age.<sup>12</sup>

Another European study examined survival among patients with HCV infection who had cirrhosis. For patients with compensated cirrhosis, survival was 91% after 5 years and 79% after 10 years. However, for patients who developed decompensated cirrhosis, 5 year survival fell to 50%.<sup>1</sup>

## Molecular biology -----

**Virology** - HCV is an enveloped, positive single-strand RNA virus classified as a separate genus in the Flaviviridae family. The genome contains approximately 9,500 nucleotides and encodes a single polypeptide precursor of about 3,000 amino acids. The precursor is cleaved both during and after translation by cellular and viral proteases to yield a highly-conserved core protein, two outer envelope glycoproteins, two different proteases, a nucleotide triphosphatase, an RNA helicase, an RNA polymerase, and a few other proteins with unknown functions.<sup>13</sup>

HCV is classified according to genotype, subtype, and isolate. There are currently six main HCV genotypes. Genotypes are defined by the more conserved regions of the genome.<sup>13</sup> Different genotypes vary by 30% or more at the nucleotide

level and by 25% to 30% at the amino acid level. Each HCV genotype consists of 1-13 subtypes that generally differ in nucleotide sequence by 20%; currently about 70 subtypes are recognized. The nucleotide sequence within a subtype is not fixed; up to 10% of the nucleotides can vary.<sup>14, 15</sup>

It is estimated that persistent HCV infection produces virions at a rate of at least  $10^{11}$  per day, this is approximately ten times the daily production of HIV.<sup>16,17</sup> The rapid kinetics of HCV production is responsible for its highly diverse genome. In RNA viruses, errors that occur during replication are uncorrected by RNA polymerase. These errors may be lethal to the virus or can alter the nucleotide sequence with or without affecting the amino acid sequence. If the amino acid sequence changes, virulence may decrease or may

not be effected, but the change could also be advantageous to the virus. As a result, with the large daily production of virions, HCV has many opportunities to evolve and can exist as several closely related, yet distinct, clones in a single host.<sup>13</sup>

**Immune response** - Because the immune response to acute HCV is usually inadequate to terminate infection, most acute HCV infections progress to persistent infection. Studies have shown that it is possible to become re-infected with another type or subtype of HCV, even after an initial infection has been successfully cleared. Similarly, concurrent infections with multiple HCV genotypes are also possible.

Because HCV can exist in its host in different mutated forms, it may be able to resist immune neutralization. The number of distinct viral quasispecies seems to increase with the duration of infection and evolves in response to antiviral treatment.<sup>18</sup> Much like HIV which can infect CD4 cells and be stored in or replicate in other types of cells, HCV RNA has been found in extrahepatic cells, further evading the immune response. Furthermore, anti-HCV antibody and cellular responses are generally ineffective at controlling viral loads once chronic hepatitis occurs.<sup>19</sup> Vaccine research for HCV has focused on the cellular response as there is some indication that an early, strong, and broad response is associated with either spontaneous viral clearance or improved antiviral treatment outcomes.<sup>18</sup>

## Diagnosis and evaluation -----

Laboratory methods for diagnosis and evaluation of HCV infection have continued to evolve since the first HCV enzyme immunoassay antibody test became available in 1990. Two approaches are currently used: tests to detect antibodies to HCV and tests to detect the virus itself.

**Antibody tests - a) Enzyme immunoassay (EIA).** HCV infection is initially diagnosed by detecting circulating antibodies to HCV (anti-HCV antibody). The EIA method is synonymous with the enzyme-linked immunosorbent assay or ELISA method. EIA tests for anti-HCV antibody have evolved from first generation (EIA-1) to third generation assays (EIA-3). While EIA-1 tests detect IgG antibody to one viral antigen, EIA-3 tests detect antibodies to four viral antigens: one from the core region of the genome, and three from the non-structural regions.

EIA-1 tests have a sensitivity of only 70% to 80%. Specificity is poor, resulting in a false positive rate of 15% to 70%, depending on the population tested. EIA-1 tests can first detect anti-HCV antibody approximately 22 weeks following acute infection.<sup>20</sup> The EIA-1 was

replaced by a multi-antigen second generation test (EIA-2) in 1992.

The EIA-2 has a sensitivity of 92% to 95% and has improved specificity when compared to the EIA-1. EIA-2 tests employ several nonstructural or composite protein antigens and an antigen from the HCV core region, shortening the average time from infection to detection of antibody to 10 weeks. The EIA-2 has a positive predictive value of nearly 95% when used to test persons who have risk factors for HCV infection.<sup>1</sup> For persons without HCV risk factors, the positive predictive value of the EIA-2 is much lower, ranging from 25% to 60%.<sup>1</sup>

The EIA-3 has greater sensitivity (up to 97%) and slightly improved specificity compared to the EIA-2. False positive results, although less frequent, are more likely to occur either among persons with no risk factors for HCV infection and who have normal ALT levels or among persons who have autoimmune disorders. Up to 20% of patients with autoimmune hepatitis may have a false positive anti-HCV antibody result.<sup>21</sup> Because of their greater sensitivity, EIA-3 tests

detect anti-HCV antibody approximately 9 days earlier than EIA-2 tests.<sup>20</sup>

**b) Recombinant immunoblot assay (RIBA).** The RIBA methodology detects anti-HCV antibody using either a nitrocellulose or nylon strip coated with four HCV antigens. If two or more of the four antigens react to a patient's serum, the result is considered positive; the result is indeterminate if only one antigen reacts. The sensitivity of the RIBA is similar to the EIA-2 and EIA-3; however, the RIBA is more specific, making false-positive results unusual. False-negative results have been seen in immune compromised patients, and false-positive tests occur occasionally among patients with autoimmune disorders. A person may have a nonspecific RIBA (single band reactivity) as a result of acute HCV infection, past cleared HCV infection, or underlying immune suppression.<sup>22</sup> A nonspecific RIBA result may also be due to infection with an uncommon HCV genotype that is not well represented by the antigens included in the assay.<sup>5</sup> In general, patients with nonspecific RIBA results should undergo additional evaluation including a test for HCV RNA or a repeat RIBA after 2 or more months.<sup>4</sup>

When used as a supplemental test, 90% of patients with liver disease who have a reactive HCV EIA are RIBA positive. In contrast, less than 50% of low risk blood donors with reactive EIA results are confirmed by RIBA. Generally, patients having a reactive EIA and a negative RIBA are considered to have a false-positive EIA.<sup>22</sup>

**HCV RNA detection** - There are two types of HCV RNA tests: qualitative and quantitative. Qualitative tests are used to detect the presence of HCV RNA, while quantitative tests are used to measure the burden of viral RNA. Quantitative HCV tests are less sensitive than qualitative tests and should not be used for initial HCV evaluation or screening; their main role is to assess viral load as a measure of response to antiviral treatment.

Because HCV may be present in low levels in serum, qualitative or quantitative HCV RNA

testing requires that HCV RNA be amplified or hybridized. Two methods are currently used: reverse transcriptase polymerase chain reaction (RT-PCR) and branched-chain DNA (bDNA). Both RT-PCR and bDNA have limitations. RT-PCR is highly sensitive, detecting as few as 100 to 1000 copies of HCV per mL. However, RT-PCR has significant inter- and intra-laboratory variations. The American College of Pathologists proficiency program found that incorrect HCV RNA results were reported by 5% to 87% of laboratories.<sup>23</sup> In comparison, bDNA is precise, reproducible, and can be standardized. Unfortunately, bDNA is much less sensitive than RT-PCR; bDNA can detect HCV RNA only when the viral load reaches  $\geq 200,000$  copies/mL.

Qualitative HCV RNA assays are reported as either positive or negative. The RT-PCR method is most useful because of its high sensitivity. Qualitative testing can be used to diagnose HCV infection in the absence of anti-HCV antibody due to early acute infection or immune compromise. The presence of HCV RNA can also be used to diagnose vertical HCV transmission from a mother to her infant, where an infant may remain anti-HCV antibody positive for up to 12 months as a result of passive transfer of maternal antibody.<sup>24</sup>

Either RT-PCR or bDNA test methods can be used to quantify the HCV RNA load. Since the sensitivity of quantitative testing is lower than that of qualitative testing, negative quantitative results do not rule-out low level viremia (which could be detected with a qualitative RT-PCR). HCV RNA titers have been found to be relatively stable during untreated persistent HCV infection and quantitative HCV RNA testing has become an important tool for management of persistent HCV infection.<sup>23</sup>

**Screening procedures** - When evaluating a patient for possible HCV infection, initial testing should include an EIA-2 or EIA-3 and a serum ALT. A reactive EIA should be repeated and, if still reactive, followed with a supplemental test – either a RIBA or qualitative RT-PCR. Current (acute or persistent) HCV infection is confirmed if the RT-PCR is positive. Resolved HCV infection is confirmed if the RT-PCR is negative and the RIBA is positive. Indications for screening are discussed below in “Secondary prevention of HCV infection.”

**HCV genotype determination** - When HCV RNA is detected, genotyping can be performed; several methods of varying complexity have been used. Genotyping is important in clinical trials because certain genotypes and subtypes may respond differently to therapeutic regimens that are under investigation.

## Transmission -----

HCV is transmitted parenterally like human immunodeficiency virus (HIV) and hepatitis B virus (HBV). Although all three viruses can be transmitted by similar means, the efficiency of HCV transmission is significantly different than that of HIV or HBV. Percutaneous exposure through blood transfusion or injecting-drug use are the most efficient means for HCV transmission. **With the advent of blood screening for anti-HCV antibody, the risk of posttransfusion HCV infection has been nearly eliminated in the United States.** HCV is inefficiently transmitted via needle stick, intranasal drug use, or hemodialysis. Sexual and perinatal transmission of HCV can occur but are much less efficient than for HIV or HBV.<sup>4</sup>

**Blood or blood product transfusion** - Prior to 1990, HCV-contaminated blood and blood products were an important source of HCV transmission. Up to 90% of persons with hemophilia who received factor concentrates prior to 1987 became anti-HCV antibody positive. Since 1990, all units of blood in the United States are screened for anti-HCV antibodies. Today, the risk of posttransfusion HCV infection is estimated to be 0.001% per unit of blood (i.e., 1 per 100,000).<sup>25</sup> Clotting factor concentrates now undergo viral inactivation procedures that have essentially eliminated the risk of HCV infection from these products.

**Injecting-drug use** - Since blood and blood products are tested for anti-HCV antibody, the majority of new HCV infections in the United States are now attributed to injecting-drug use. CDC estimates that 72% to 86% of current injecting-drug users are anti-HCV antibody positive. **Injecting-drug use may be a more efficient means of transmitting HCV than HBV or HIV.** In one study, persons with a history of <1 year of injecting-drug use had a higher prevalence of antibodies to HCV (69%) than to HBV (41%) or HIV (14%).<sup>26</sup> Other studies have found similar or higher anti-HCV antibody prevalence among injecting-drug users.<sup>27</sup> The high prevalence of HCV infection among drug users is attributed to the cumulative effects of frequent and multiple exposure and a large pool of needle-sharing partners with persistent HCV infection.

**Other percutaneous exposures - a) Occupational exposure.** For health-care and other workers, the average risk of becoming infected with HCV following a needle stick or sharps injury involving a known HCV-positive source is estimated to be 1.8% (range, 0% to 7%).<sup>4</sup> One study, using HCV RNA detection methods, reported an incidence of 10%.<sup>28</sup> This contrasts with transmission rates of 10% to 40% for HBV and 0.3% for HIV following needle stick injuries involving HbsAg- or HIV-positive blood, respectively.<sup>29,30</sup> Factors that influence the risk of HCV infection after a needle

stick injury include the quantity of blood transferred, the HCV RNA titer of the blood, the depth of inoculation, and type of needle (solid or hollow cannula).<sup>31</sup>

***b) Tattooing, acupuncture, and body piercing.*** These activities have not been associated with HCV infection in the United States, and HCV transmission from such exposures has not been confirmed.<sup>1, 32</sup>

***Household nonsexual exposure*** - There is conflicting evidence of HCV transmission within the household setting, excluding sexual or vertical routes of transmission.<sup>33</sup> The prevalence of HCV infection increases among family members in proportion to the disease severity of the index patient.<sup>9</sup> Actual risk of transmission has been difficult to assess because of confounding from other risk factors that may be common to all household members. Possible routes of household transmission are unknown but could include contact to minute amounts of blood on toothbrushes, razors, dental appliances, and nail-grooming equipment.<sup>27</sup>

***Sexual transmission*** - Although sexual transmission of HCV can occur, data on transmissibility is inconsistent; however, sexual transmission is inefficient and much less likely than transmission of HIV or HBV.<sup>27</sup> Studies that controlled for other potential sources of HCV (e.g., injecting-drug use) rarely found evidence of sexual transmission. HCV RNA has generally not been found in semen, vaginal fluid, urine, or

stool, although low amounts of HCV RNA have been found in saliva. The frequency of concordant HCV-infected sexual partners (0% to 4.4%) is similar among heterosexual and homosexual couples, suggesting that homosexual transmission may occur at a similar rate as heterosexual transmission.<sup>4</sup> Anti-HCV antibodies have been found in 1% to 12% of prostitutes. It is unclear whether the risk of HCV among prostitutes is due to their sexual practices or to other factors like injecting-drug use.<sup>28, 31</sup>

***Vertical transmission*** - HCV can be transmitted from an HCV-infected mother to her infant. Vertical transmission of HCV occurs less frequently than HBV.<sup>27</sup> The average prevalence of HCV infection among infants born to HIV-negative HCV-positive pregnant women was 5% to 6%.<sup>4, 34</sup>

The role of HIV co-infection and HCV RNA load in vertical transmission is conflicting. Some studies have suggested a link between transmission and being HIV-positive or having a high HCV RNA load, while others have found HCV vertical transmission rates were similar regardless of HIV status or HCV RNA load.<sup>34</sup> No association between breast-feeding and HCV transmission has been documented, although HCV RNA has been found in breast milk of some HCV-positive mothers. Lack of transmission through breast milk may be due to the small amount of HCV present and the enteric exposure to the virus.<sup>27</sup>

# Epidemiology of HCV infection

**World** - In 1997, the World Health Organization estimated that 3% of the world's population was infected with HCV. By this approximation, there are more than 170 million persons with persistent HCV infection.<sup>35</sup>

**United States** - Based on data from the Third National Health and Nutrition Examination Survey, the CDC estimated the prevalence of HCV infection in the United States to be 1.8%; this corresponds to an estimated 3.9 million persistent HCV infections.<sup>36</sup> The estimated incidence of acute HCV infection was relatively stable throughout the 1980s peaking at an estimated 180,000 new infections in 1984. Since 1989, the incidence of acute HCV infection in the United States has declined by more than 80%. In 1997, 3,816 acute cases of either HCV infection or non-A, non-B hepatitis were reported to the CDC.<sup>36</sup> This is a decline from 4,576 acute cases of HCV infection or non-A, non-B hepatitis that were reported to the CDC in 1995. After adjusting for underreporting, the CDC estimated that there were 36,000 new HCV infections in 1996, but that only 30% to 40% of these persons developed acute symptoms.<sup>4</sup>

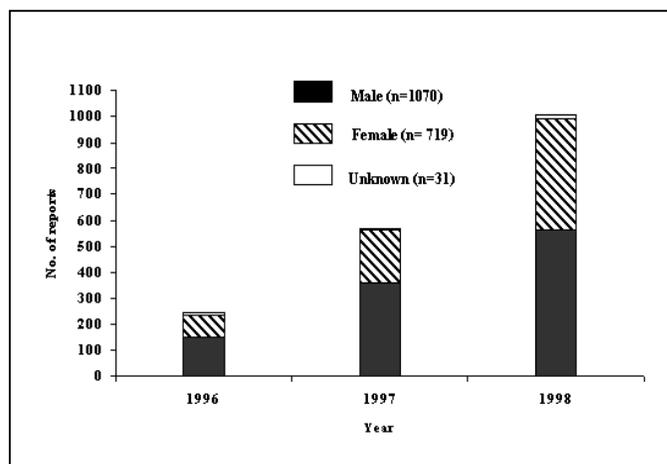
**Alaska** - The CDC estimate of nationwide HCV prevalence (1.8%) can be applied to the 1998 provisional Alaska population, 621,400. This results in an estimated prevalence of 11,185 Alaskans with HCV infection (621,400 times 1.8%). There are no data which could be used to examine the validity of this prevalence estimate and it therefore should be considered, at best, as only a rough estimate of HCV prevalence in Alaska. Based on the total number of HCV infections reported in Alaska (see below) and the rough estimate of prevalence, it is very likely that a large number of persons with persistent HCV infection either have not been tested or, if tested, have not been reported to public health.

HCV infection was made a reportable condition in Alaska in 1996. Both health-care providers and laboratories are required to report patients

with HCV infection to the Section of Epidemiology. Reports include persons with acute disease, persistent infection, and chronic disease – thus, the following data reflect *both* persistent and acute infections. The data for Alaska are the numbers of persons who were reported to have a test result(s) showing HCV infection; most of these persons have persistent HCV infection. Prevalence is the *total* number of cases of a disease in a population at a specified time (i.e., newly found acute and persistent infections plus previously found persistent infections still in the population). Because Alaska data include persons reported only since January 1996 and it is likely that many persons with persistent HCV infection have not yet sought medical care or anti-HCV antibody testing, the data are an incomplete measurement of the true prevalence of HCV infection.

**a) Age, sex, and year of report.** Between January 1, 1996 and December 31, 1998, there were 1,820 cases of HCV infection reported in Alaska. The number of reports steadily increased by year: there were 246, 570, and 1004 reports in 1996, 1997, and 1998, respectively (Figure 2).

**Figure 2. Reported HCV cases, by sex and year, Alaska, 1996-1998**



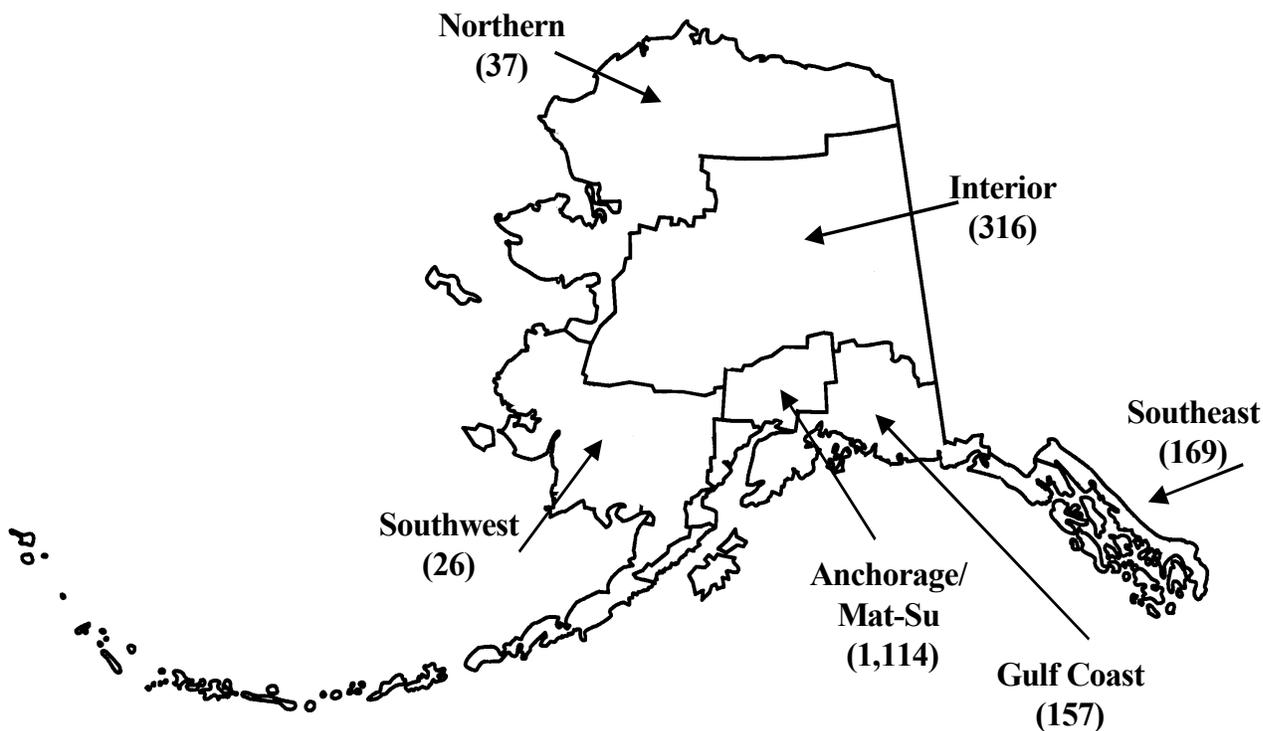
Overall, 1,070 (59%) of the persons reported were male, 719 (40%) were female, and 31 (2%) had no sex reported. Almost half (47%) of the cases were 40-49 years of age, and nearly one-third (534 or 29%) of the reported cases were 40-49 year-old men (Table 1). The median age of cases was 42 years.

**b) Place of residence.** Of the reported cases, 1,114 (61%) resided in the Anchorage or Mat-Su area, 316 (17%) resided in interior Alaska, 169 (9%) resided in the Southeast, 157 (9%) resided in the Gulf Coast, 37 (2%) resided in the Northern area, and 26 (1%) resided in the Southwest (Figure 3).

**Table 1. Age and sex of reported HCV cases, Alaska, 1996-1998**

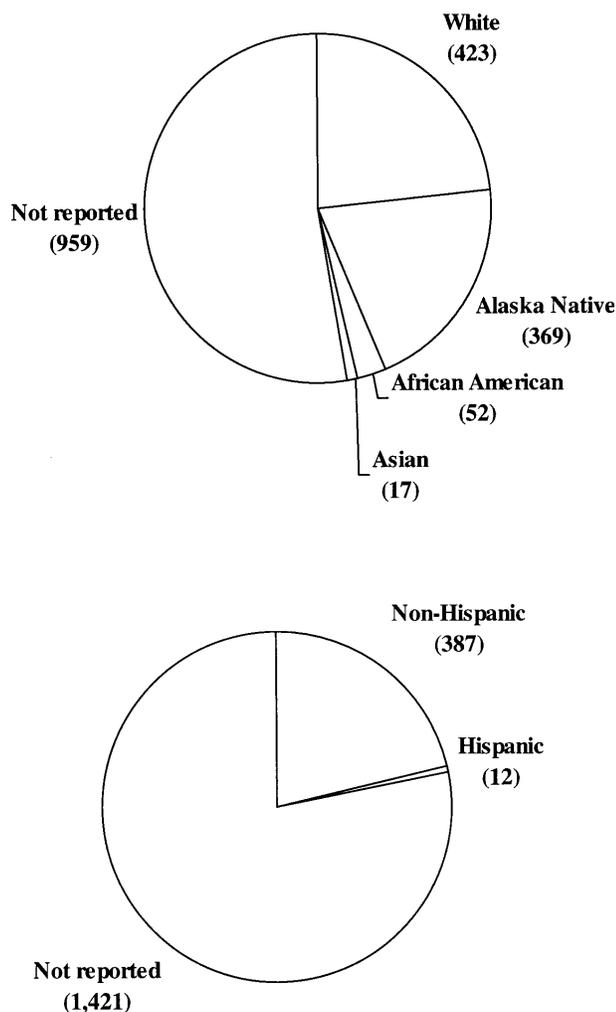
<i>Age group (years)</i>	<i>Sex</i>			<i>Total</i>
	<i>male</i>	<i>female</i>	<i>unreported</i>	
0-9	5	5	0	10
10-19	1	12	0	13
20-29	34	52	2	88
30-39	298	242	13	553
40-49	534	308	12	854
50-59	110	51	1	162
≥60	33	21	0	54
unreported	55	28	3	86
Total	1,070	719	31	1,820

**Figure 3. Place of residence of reported HCV cases, 1996-1998, Alaska**



**c) Race and ethnicity.** Information on race and ethnicity was frequently not reported: race was reported for 861 cases (47%), and ethnicity (if the person was of Hispanic ethnicity or not) was reported for 399 cases (22%). Among persons whose race was reported, 423 were white, 369 were Alaska Native or Native American, 52 were African American, and 17 were Asian (Figure 4). For persons whose ethnicity was reported, 387 were non-Hispanic, and 12 were of Hispanic origin (Figure 4).

**Figure 4. Reported HCV cases, by race and ethnicity, Alaska, 1996-1998**



**d) Testing conducted through the state laboratory.** The State Virology Laboratory uses a single EIA-2 to test for anti-HCV antibody. Supplemental testing (such as RIBA or a qualitative HCV RNA assay), which currently is not available at the state laboratory, should be done for all patients with a reactive EIA-2. Supplemental test results, if any, were not obtained from the primary health care providers. In addition, repeat tests of the same patient (whether ordered by one health-care provider or multiple providers and whether the results were reactive or not) have not been eliminated – thus the number of specimens tested is greater than the number of persons tested. Furthermore, code numbers rather than names were used to identify some of the specimens tested by the state laboratory; these specimens were included in the following data, but were not included in the statewide data reported above in a) through c).

From January 1, 1996 through December 31, 1998, 5,244 specimens were tested, and 772 (15%) were reactive. Of 2,781 males tested, 18% (510) were reactive, while 11% (256) of 2,400 females had reactive tests (sex was not indicated for 63 specimens). During 1996-1998, 179 of the reactive results were coded (i.e., unnamed) specimens.

Although the number of anti-HCV antibody tests done at the State Virology Laboratory has increased each year, the proportion with reactive results has declined. The percent reactive was 28% (140/507) for 1996, 16% (256/1,614) for 1997, and 12% (376/3,123) for 1998.

The median age of persons tested was 33 years, although the median age of persons who had a reactive result was 39 years. The majority of persons tested were from 10 to 49 years of age (89%; 4,660/5,244 tests); however, the majority of reactive results were persons from 30 to 49 years of age (82%; 635/772 reactive tests). Only 3% of persons (67/2,183) from 10 and 29 years of age had reactive EIA-2 results.

The distribution of place of residence for persons with a reactive test at the state laboratory was similar to that of the statewide data. Among reactive tests, 489 (63%) were from the Anchorage/Mat-Su area, 116 (15%) were from the Interior, 90 (12%) were from the Gulf Coast, 70 (9%) were from the Southeast, 3 (0.4%) were from the Southwest, and 2 (0.3%) were from the Northern region.

The distribution of specimens submitted did not mirror the distribution of reactive results. The Anchorage/Mat-Su region comprised 57% (2,981) of all submissions. The Southeast region submitted the next largest proportion of specimens, with 20% (1,068) of the total. This was followed by submissions from the Gulf Coast and Interior regions, with 11% (590) and 10% (544) respectively, of the total. The Northern and Southwest regions submitted the

fewest specimens to the state laboratory: 1% (31) of submissions were from the Northern region, while 0.4% (23) of submissions were from the Southwest region.

*e) Other aspects of HCV infection in Alaska.* A cohort of 501 persons who were current users of illicit drugs in Anchorage was tested for anti-HCV antibody. Results published in 1997 showed that 81% of those who reported being injecting-drug users had a positive EIA-2.<sup>37</sup> In another study, 375 persons with persistent HCV infection were enrolled in a study at the Alaska Native Medical Center. In this cohort, 63% gave a history of injecting-drug use.<sup>38</sup> Finally, 16 (55%) of 29 anti-HCV antibody positive patients cared for by a private practice gastroenterologist in Anchorage had a history of injecting-drug use (Section of Epidemiology, unpublished data).

## Primary prevention of HCV infection -----

**At this time, no vaccine is available to protect against HCV infection. In addition, post-exposure prophylaxis with immune globulin is not effective in preventing HCV transmission.** Interferon and other antiviral agents used for treating persistent HCV infection have not been evaluated for postexposure use.

**Blood, organ, and tissue donation** - All immune globulin products commercially available in the United States must be HCV RNA-negative or undergo viral inactivation before release.<sup>3</sup> In addition, since 1992 the United States blood and blood product supply has been screened by anti-HCV EIA. The CDC recommends that all organ, tissue, or semen donors be screened for HCV infection. Infected persons should not donate blood, tissues, body organs, or semen. Prospective blood donors with a history of injecting-drug use should not be permitted to donate.

**Injecting-drug use** - Injecting-drug use is currently the most commonly cited risk factor for HCV transmission. In addition, there is evidence that acquisition of HCV infection can occur rapidly among persons who initiate using injecting-drugs. Prevention of injecting-drug use, programs that encourage injecting-drug users to stop using and seek treatment, and programs that encourage harm reduction techniques (e.g., needle or syringe exchanges for persons who continue to inject) all reduce the risk of HCV transmission.

**Health-care settings** - Universal precautions should be used consistently. There are no recommendations to restrict HCV-positive health-care workers, because the risk of HCV transmission from an infected health-care worker to a patient appears to be low. Follow-up for workers potentially exposed to HCV is discussed below under "Secondary prevention of HCV infection."

**Sexual transmission** - There are no specific recommendations for HCV-infected persons in long-term monogamous relationships to change their sexual practices, because the risk of transmission appears to be low. However, couples should be informed of the potential for transmission so they can decide if they wish to take precautions. Infected and uninfected persons with multiple sexual partners should be encouraged to practice safer sex behaviors, namely reducing their number of sex partners and using latex condoms.

**Household exposure** - In households with an HCV-infected member, sharing toothbrushes and razors should be avoided and open wounds should be covered. Avoiding close contact with HCV-infected persons is unnecessary.

**Vertical transmission** - There are no recommendations for women who have HCV infection to avoid pregnancy or breast feeding.

**Vaccine research** - The National Institutes of Health has identified the development of an effective and safe vaccine as one of the most important areas for future research and prevention of HCV infection.<sup>1</sup> Although research in this area is ongoing, it is impeded by several obstacles: the lack of an *in vitro* replication assay, lack of a susceptible animal model aside from the chimpanzee, and lack of purified HCV antigens. In addition, clinical studies have not yet documented which types of immune response can control or prevent HCV infection.<sup>18</sup>

## **Secondary prevention of HCV infection-----**

Secondary prevention activities reduce the risk for liver and other chronic disease complications among persons who have HCV infection. To be successful, these activities first must identify persons with HCV infection. Because there are a large number of persons with persistent HCV infection in the United States, identification of these persons is a major secondary prevention activity. Effective identification requires that routine testing for HCV infection be provided to persons potentially infected. Once identified, persons with HCV infection must then receive appropriate medical management and antiviral treatment.

**Routine HCV testing** - The CDC has developed guidelines for offering HCV testing to those persons most likely infected with HCV (Table 2). In addition, testing can be provided to any person wishing to know their HCV status. A detailed rationale for and explanation of the recommendations outlined in Table 2 can be found in a CDC publication.<sup>4</sup>

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**Table 2. Persons who should be routinely tested for HCV infection\***

- Persons who ever injected illegal drugs, including former users, infrequent users, and current users.
- Persons with certain medical conditions, including
  - persons who received clotting factor concentrates produced before 1987;
  - persons who received chronic (long-term) hemodialysis; and
  - persons who have persistently elevated ALT levels or other biochemical evidence of liver disease.
- Certain recipients of transfusions or organ transplants, including
  - persons who were notified that they received blood from a donor who later tested positive for HCV;
  - persons who received, prior to July 1992, a blood or blood component transfusion or an organ transplant.
- Persons who should be tested for HCV infection based on a specific exposure, including
  - health-care, emergency medical, and public safety workers after needle sticks, sharps, or mucosal exposure to HCV-positive blood; and
  - children born to HCV-positive women.

\* from Ref. 4. Not included in this table is screening of blood, plasma, organ, tissue, and semen donors.

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When testing is done for health-care, emergency medical, or public safety workers after a possible HCV exposure (as described in Table 2), the exposed person should have baseline and follow-up testing for anti-HCV antibody and ALT. If baseline testing is negative, follow-up tests should be done at 4-6 months after exposure (or, if earlier results are desired, qualitative HCV RNA testing can be ordered at 4-6 weeks). The source should have baseline testing for anti-HCV antibody. All reactive EIA results should be repeated and, if still reactive, confirmed with supplemental testing.

***Persons not routinely tested*** - Routine testing for HCV is unlikely to identify persons with HCV infection if none of the factors described in Table 2 are present. In the absence of risk factors, the CDC does not recommend routine HCV testing of health-care workers, emergency medical workers, public safety workers, pregnant women, household (nonsexual) contacts of persons with HCV infection, or the general public.<sup>4</sup> According to the CDC, the need for routine testing of certain other persons is uncertain. This includes recipients of tissue transplants, intranasal cocaine and other noninjecting-drug users, persons with tattoos or body piercing, persons with multiple sex partners or sexually transmitted disease(s), and long-term monogamous sex partners of HCV-positive persons.<sup>4</sup>

***Management of persons with HCV infection -***

Because the indications for and practice of antiviral therapy are rapidly changing, decisions about medical management are best made by appropriate specialists. Irrespective of medical decisions, persons with persistent HCV infection need to prevent further harm to their liver and reduce the risk of transmitting HCV to others. To protect their liver, persons with HCV infection should:

- not drink alcohol; and
- not take *any* medicines, including over-the-counter preparations and herbal remedies, without checking with their doctor.

In addition, persons with persistent infection who have evidence of chronic hepatitis should be vaccinated against hepatitis A.

To reduce the risk of transmitting HCV to others, persons with HCV infection should:

- not donate blood, body organs or tissue, or semen;
- not share toothbrushes, razors, dental appliances, or other personal care items that might have blood on them; and
- keep cuts and sores on the skin covered.

The CDC has not recommended that HCV-positive women avoid either becoming pregnant or breastfeeding their infant(s). Potential new parents should be advised that there is approximately a 5% risk of HCV being passed from an HCV-positive mother to her infant. Other important information that should be discussed is described by the CDC.<sup>4</sup> HCV-positive persons with a long-term monogamous sexual partner do not need to alter their sexual practices. However, they should be encouraged to discuss the risk with their partner and use barrier precautions (i.e., latex condoms) to reduce the already low risk of transmission.

## Resources

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Like many other chronic diseases, such as diabetes, cancer, or asthma, patients with persistent HCV infection often have questions and concerns about their condition. The Alaska Hepatitis C Coalition, a group of persons interested in HCV, or who have persistent HCV infection, provides information, conducts support groups, and works to improve primary and secondary prevention. The coalition can help persons make contact with other grass-roots HCV organizations in the state. Persons interested in reaching the coalition should call the Section of Epidemiology at 907-269-8000.

A variety of other resources are available, including:

1. American Liver Foundation  
1425 Pompton Avenue  
Cedar Grove, NJ 07009  
Tel: (800) 465-4837 or (888) 443-7222  
Fax: (201) 256-3214  
E-mail: [info@liverfoundation.org](mailto:info@liverfoundation.org)  
Home page: <http://www.liverfoundation.org>

The American Liver Foundation promotes awareness and supports research on liver disease; disseminates information about liver wellness, liver disease, and prevention of liver disease with audiovisual and printed materials, seminars, and training programs; promotes organ donation; encourages vaccination against hepatitis B; serves as trustee of transplant funds; and offers support groups through local chapters. They publish a member newsletter (Progress), a clinical newsletter for physicians (Liver Update), and pamphlets and fact sheets about liver diseases, transplantation, organ donation, and prevention.

2. Hepatitis Foundation International  
30 Sunrise Terrace  
Cedar Grove, NJ 07009-1423  
Tel: (201) 239-1035 or (800) 891-0707  
Fax: (201) 857-5044  
E-mail: [hfi@intac.com](mailto:hfi@intac.com)  
Home page: <http://www.hepfi.org>

Hepatitis Foundation International fosters worldwide awareness about the prevention, diagnosis, and treatment of viral hepatitis; provides patient and professional education programs; distributes publications; and supports research. A unique service is the Patient Advocacy/Information Telecommunications System, a phone support network that enables patients to talk to others with similar concerns. Publications include a newsletter (Hepatitis Alert), poster (Take Care of Your Liver), and the following fact sheets:

- Caring for Your Liver
- Diagnosis and Treatment for Hepatitis
- Hepatitis C
- Hepatitis D, E & F
- Hepatitis Statistics
- Research Advances in Hepatitis
- Vaccines for Hepatitis A and B

3. U.S. Centers for Disease Control and Prevention (CDC)  
CDC website for HCV:  
<http://www.cdc.gov/ncidod/diseases/hepatitis/c/index.htm>

This website includes access to a fact sheet, a comprehensive set of questions and answers about HCV infection, and several CDC publications on HCV (for patients and health care providers). In addition, CDC has an audiotape for health-care providers on HCV clinical management that can be ordered from the website as well as the following pamphlets:

- If You Have Hepatitis C
- Hepatitis C Prevention
- If You Were Notified That You Received Blood Possibly Infectious for Hepatitis C Virus or If You Received Blood Before July 1992

4. The National Institutes of Health Home page:  
<http://www.nih.gov>

Users can access a brochure for patients with HCV infection (What do I need to know about hepatitis C?) as well as several documents for health-care providers including:

- A "State-of-the-Art" Conference - Hepatitis C: A Meeting Ground for the Generalist and the Specialist (March 18, 1999)
- Chronic Hepatitis C: Disease Management (September 20, 1998)
- Management of Hepatitis C (March 1997)

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