

Chapter 3: Hepatitis C - Epidemiology, transmission and natural history

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Epidemiology

Hepatitis C is a disease with a significant global impact. According to the World Health Organization there are 170 million people infected with the hepatitis C virus (HCV), corresponding to 3% of the world's total population. There are considerable regional differences. In some countries, e.g., Egypt, the prevalence is as high as 20%. In Africa and the Western Pacific the prevalence is significantly higher than in North America and Europe (Anonymous 2004).

It is estimated that there are 2-5 million HCV-positive persons in Europe. The prevalence of HCV-antibodies in otherwise healthy blood donors is approximately 1.6% in the United States, 1.15% in Italy, 0.4% in Germany, and 0.23% in Scandinavia (Anonymous 2004). The number of patients actually HCV RNA positive is estimated to be around 80 to 90% of all HCV-antibody positive persons. Certain groups are preferentially affected: The highest risk factor in most instances is injection drug use. But patients undergoing hemodialysis and persons who received blood transfusions before 1991 are at risk also. In Europe and the United States chronic hepatitis C is the most common chronic liver disease. The majority of liver transplants performed in these regions are for chronic HCV.

It is difficult to determine the number of new HCV infections, as most acute cases will not be noticed clinically. Fewer than 25% of acute cases of hepatitis C are clinically apparent. In addition, the age of infection upon diagnosis is not possible to determine in most cases. Nevertheless, it has to be assumed that the number of new infections has considerably decreased over the past decades. For the United States it is estimated that the number of new cases of acute HCV infection has fallen from approximately 230,000 per year in the 1980s to about 20,000 cases per year currently (Wasley 2008). This decrease is primarily associated with reduced infections in injection drug users, a probable consequence of changes in injection practices motivated by education about human immunodeficiency virus (HIV) transmission. Transfusion-associated hepatitis C has had little impact on this decline, as the number of cases has been reduced almost to zero.

Transmission

Parenteral exposure to the hepatitis C virus is the most efficient means of transmission. Accordingly, the majority of patients infected with HCV in Europe and the United States acquired the disease through intravenous drug use or blood transfusion. The latter has become rare since routine testing of the blood supply for HCV began in the early 1990s. Other types of parenteral exposure are important in specific regions in the world.

The following possible routes of infection have been identified in anti-HCV-positive blood donors (in descending order of transmission risk):

- Injection drug use
- Blood transfusion
- Sex with an intravenous drug user
- Having been in jail more than three days
- Religious scarification
- Having been struck or cut with a bloody object
- Pierced ears or body parts
- Immunoglobulin injection

Very often in patients with newly diagnosed HCV infection no clear risk factor can be identified.

Injection drug use

Injection drug use has been the most commonly identified source of acute HCV infection. It is estimated that most newly acquired infections occur in individuals who have injected illegal drugs. The seroprevalence of anti-HCV antibodies in groups of intravenous drug users may be up to 70% with considerable variation depending on factors such as region, risk behaviour, socioeconomic status and others, underscoring the efficiency of transmission via direct blood contact (Sutton 2008). HCV infection also has been associated with a history of intranasal cocaine use, presumably due to blood on shared straws or other sniffing paraphernalia.

Blood transfusion

In the past, blood transfusion or use of other blood products was a major risk factor for transmission of HCV. In some historic cohorts 10% or more of patients who received blood transfusions were infected with hepatitis C (Alter 1989). However, blood donor screening for HCV since the early 1990s has nearly eliminated this transmission route. Blood donors are screened for anti-HCV antibodies and HCV RNA – at least in developed countries. The risk is now estimated to be between 1:500,000 and 1:1,000,000 units (Pomper 2003).

In cohorts of multiply transfused patients such as hemophiliacs, over 90% of patients were infected with hepatitis C in the past (Francois 1993). Since the use of routine inactivated virus (e.g., heat inactivation or pasteurization) or recombinant clotting factors, new cases of hepatitis C infection have become uncommon in these patients.

Organ transplantation

Transplant recipients who receive organs from HCV-positive donors have a high risk of acquiring HCV infection. Transmission rates in different cohorts vary from 30 to 80% (Pereira 1991; Roth 1994). Therefore, most transplant organisations have developed strategies for screening and selective utilization of organs from anti-HCV positive donors.

Sexual or household contact

Usual household contacts do not pose a risk of HCV transmission. The efficiency of HCV transmission by sexual contact is very low. However, there is no doubt that sexual transmission of hepatitis C is possible.

The exact risk of HCV transmission in monogamous heterosexual relationships has been difficult to determine. It appears that the risk in long-term partnerships is very low. In prospective cohorts of monogamous, heterosexual couples, there was a long-term transmission risk of 0.01% or lower (Vandelli 2004). Factors that may increase the risk of HCV infection include greater numbers of sex partners, history of sexually transmitted diseases, and failure to use a condom. Whether underlying HIV infection increases the risk of heterosexual HCV transmission to an uninfected partner is unclear. Very often it is difficult to rule out the possibility that transmission results from risk factors other than sexual exposure.

Outbreaks of cases of acute hepatitis C in several cities in Europe and the United States among men who have sex with men (MSM) have focused attention on sexual transmission of HCV. There is clear evidence that no other route than unprotected sex can account for the transmission of HCV. Unprotected anal sex, fisting, having many sex partners in a short time period, and a concomitant sexually transmitted disease were identified risk factors (Danta 2007). It appears that mucosal damage is a prerequisite for HCV transmission. According to these observations, the seroprevalence of HCV in MSM ranges from about 4 to 8%, which is higher than the HCV prevalence reported for general European populations.

Patients with acute or chronic HCV infection should be advised that transmission to sexual contacts is a possibility, although the risk is extremely low in heterosexual relationships. It is likely that the use of condoms will lower the risk of sexual transmission further. However, in most countries there are no firm recommendations to use barrier precautions in stable monogamous sexual partnerships. The transmission risk in MSM is considerably higher so that – in conjunction with the risk of other sexually transmitted diseases – safer sex practices should be advised in this group.

Perinatal transmission

The risk of perinatal transmission of HCV in HCV RNA positive mothers is estimated to be 5% or less (Ohto 1994). In mothers coinfecting with HIV this risk correlates with immunosuppression and has been described to reach up to 20%. Today, there are no specific recommendations for prevention of perinatal transmission (Pembrey 2005). Caesarean section has not been shown to reduce the transmission risk. There is no evidence that breastfeeding is a risk for infection among infants born to HCV-infected women. Early diagnosis of infection in newborns requires HCV RNA testing since anti-HCV antibodies are passively transferred from the mother.

Hemodialysis

Patients who participate in chronic hemodialysis programs are at increased risk for hepatitis C. The prevalence of HCV antibodies in such patients reaches 15%, although it has declined in recent years (Fissell 2004). A number of risk factors have been identified for HCV infection among dialysis patients. These include blood transfusions, the duration of hemodialysis, the prevalence of HCV infection in the dialysis unit, and the type of dialysis. The risk is higher with in-hospital hemodialysis as opposed to peritoneal dialysis. The best strategy to prevent hemodialysis-associated HCV transmission is subject to debate.

Other rare transmission routes

Rare sources of percutaneous transmission of HCV are contaminated equipment used during medical procedures, procedures involved in traditional medicine (e.g., scarification, cupping), tattooing, and body piercing (Haley 2001). All these routes bear the potential of transmitting HCV. However, in most instances it is not clear if the risk is due to the procedure itself, or whether there are possible contacts with persons involved who are HCV-positive. In addition, transmission via these routes is so rare that persons with exposure are not at increased risk for acquiring hepatitis C.

Needle-stick injury

There is some risk of HCV transmission for health care workers after unintentional needle stick injury or exposure to other sharp objects. The incidence of seroconversion after exposure to an HCV-positive source is generally estimated to be less than 2% (Anonymous 2001). However, data are divergent and figures ranging from 0 to 10% can be found (Mitsui 1992). Exposure of HCV to intact skin has not been associated with HCV transmission.

Clinical manifestations and natural history of HCV infection

The spectrum of clinical manifestations of HCV infection varies in acute versus chronic disease. Acute infection with HCV is most often asymptomatic. It leads to chronic infection in about 80% of cases. The manifestations of chronic HCV range from an asymptomatic state to cirrhosis, and hepatocellular carcinoma. HCV infection usually is slowly progressive. Thus, it may not result in clinically apparent liver disease in many patients if the infection is acquired later in life. Approximately 20-30% of chronically infected individuals develop cirrhosis over a 20-30 year period of time.

Acute hepatitis C

After inoculation of HCV, there is a variable incubation period. HCV RNA in blood (or liver) can be detected by PCR within several days to eight weeks (Hoofnagle 1997). Aminotransferases become elevated approximately 6-12 weeks after exposure (range 1-26 weeks). The elevation of aminotransferases varies considerably among individuals, but tends to be more than 10-30 times the upper limit of normal (typically around 800 U/l). HCV antibodies can be found for the first time around 8 weeks after exposure although in some patients it may take several months before HCV antibodies are detected by ELISA testing.

However, the majority of newly-infected patients will be asymptomatic and have a clinically nonapparent or mild course. Jaundice as a clinical feature of acute hepatitis C will be present in less than 25% of infected patients. Therefore, acute hepatitis C will not be noticed in most patients. Periodic screening for infection may be warranted in certain groups of patients who are at high risk for infection, e.g., homosexually-active patients with HIV infection.

Other symptoms that may occur are similar to those in other forms of acute viral hepatitis, including malaise, nausea, and right upper quadrant pain. In patients who

experience such symptoms of acute hepatitis, the illness typically lasts for 2-12 weeks. Along with clinical resolution of symptoms, aminotransferases levels will normalize in about 40% of patients. Loss of HCV RNA, which indicates cure from hepatitis C, occurs in fewer than 20% of patients – regardless of normalisation of aminotransferases.

Fulminant hepatic failure due to acute HCV infection is very rare. It may be more common in patients with underlying chronic hepatitis B virus infection (Chu 1999).

Chronic hepatitis C

The risk of chronic HCV infection is high. 80-100% of patients remain HCV RNA positive after acute hepatitis C (Alter 1999). Most of these will have persistently elevated liver enzymes in further follow-up. By definition, hepatitis C is regarded to be chronic after persistence of more than six months. Once chronic infection is established, there is a very low rate of spontaneous clearance.

It is unclear why infection with HCV results in chronic infection in most cases. Genetic diversity of the virus and its tendency toward rapid mutation may allow HCV to constantly escape immune recognition. Host factors may also be involved in the ability to spontaneously clear the virus. Factors that have been associated with successful HCV clearance are HCV-specific CD4 T cell responses, high titers of neutralising antibodies against HCV structural proteins, and specific HLA-DRB1 and DQB1 alleles (Lauer 2001). Infection with HCV during childhood appears to be associated with a lower risk of chronic infection, approximately 50-60% (Vogt 1999). Finally, there seem to be ethnic differences, with lower risk of chronicity in certain populations.

Most patients with chronic infection are asymptomatic or have only mild nonspecific symptoms as long as cirrhosis is not present (Lauer 2001; Merican 1993). The most frequent complaint is fatigue. Less common manifestations are nausea, weakness, myalgia, arthralgia, and weight loss. HCV infection has also been associated with cognitive impairment. All these symptoms are non-specific and do not reflect disease activity or severity (Merican 1993). Very often symptoms may be caused by other underlying diseases (e.g., depression), and it can be difficult to distinguish between different diseases. Fatigue as the most common symptom may be present in many other situations (including healthy control groups within clinical studies). Hepatitis C is rarely incapacitating.

Aminotransferase levels can vary considerably over the natural history of chronic hepatitis C. Most patients have only slight elevations of transaminases. Up to one third of patients have a normal serum ALT (Martinot-Peignoux 2001; Puoti 2002). About 25% of patients have a serum ALT concentration of more than twice normal, but usually less than 5 times above the upper limit of normal. Elevations of 10 times the upper limit of normal are very seldomly seen.

There is a poor correlation between concentrations of aminotransferases and liver histology. Even patients with normal serum ALT show histologic evidence of chronic inflammation in the majority of cases (Mathurin 1998). The degree of injury is typically minimal or mild in these patients. Accordingly, normalisation of aminotransferases after interferon therapy does not necessarily reflect histologic improvement.

Natural history

The risk of developing cirrhosis within 20 years is estimated to be around 10 to 20%, with some studies showing estimates up to 50% (de Ledinghen 2007; Poynard 1997; Sangiovanni 2006; Wiese 2000). Due to the long course of hepatitis C the exact risk is very difficult to determine, and figures are divergent for different studies and populations. In fact, chronic hepatitis C is not necessarily progressive in all affected patients. In several cohorts it has been shown that a substantial number of patients will not develop cirrhosis over a given time. It is estimated that about 30% of patients will not develop cirrhosis for at least 50 years (Poynard 1997).

Therefore, studies with short observation periods sometimes fail to show an increase in mortality. In addition, survival is generally not impaired until cirrhosis has developed. On the other hand, there is no doubt that patients with chronic hepatitis C have a high risk of cirrhosis, decompensation, and hepatocellular carcinoma in long-term follow-up. For example, in a cohort of patients with post-transfusion hepatitis C evaluated more than 20 years after transfusion 23% had chronic active hepatitis, 51% cirrhosis, and 5% hepatocellular carcinoma (Tong 1995). It is not completely understood why there are such differences in disease progression. An influence of host and viral factors has to be assumed.

Cirrhosis and hepatic decompensation

Complications of hepatitis C occur almost exclusively in patients who have developed cirrhosis. Interestingly, non-liver related mortality is higher in cirrhotic patients as well. However, cirrhosis may be very difficult to diagnose clinically, as most cirrhotic patients will be asymptomatic as long as hepatic decompensation does not occur. Findings that can be associated with cirrhosis are hepatomegaly and/or splenomegaly on physical examination, elevated serum bilirubin concentration, hyperalbuminemia, or low platelets. Other clinical findings associated with chronic liver disease may be found such as spider angiomas, Caput medusae, palmar erythema, testicular atrophy, or gynaecomastia. Most of these findings are found in less than half of cirrhotic patients, and therefore none is sufficient to establish a diagnosis of cirrhosis.

Hepatic decompensation can occur in several forms. Most common is ascites, followed by variceal bleeding, encephalopathy and jaundice. As mentioned earlier, hepatic decompensation will develop only in cirrhotic patients. However, not all patients with cirrhosis actually show signs of decompensation over time. The risk for decompensation is estimated to be close to 5% per year in cirrhotics (Poynard 1997). Once decompensation has developed the 5-year survival rate is roughly 50% (Planas 2004). For this group of patients liver transplantation is the only effective therapy.

Similar to decompensation, hepatocellular carcinoma (HCC) develops solely in patients with cirrhosis (in contrast to chronic hepatitis B). The risk for HCC has been estimated to be less than 3% per year once cirrhosis has developed (Di Bisceglie 1997; Fattovich 1997). However, HCV-associated HCC has significant impact on survival (see Chapter 21).

Elevated concentrations of alpha-fetoprotein (AFP) do not necessarily indicate HCC. AFP may be mildly elevated in chronic HCV infection (i.e., 10 to 100 ng/mL). Levels above 400 ng/mL as well as a continuous rise in AFP over time are suggestive of HCC.

Disease progression

Chronic hepatitis C has different courses among individuals. It is not completely understood why there are differences in disease progression. Several factors have been identified that may be associated with such differences. However, other factors not yet identified may also be important.

- **Age and gender:** Acquisition of HCV infection after the age of 40 to 55 may be associated with a more rapid progression of liver injury, as well as male gender (Svrtlih 2007). On the contrary, children appear to have a relatively low risk of disease progression (Child 1964). In one cohort, for example, only 1 of 37 patients with HCV RNA in serum had elevated levels of serum aminotransferases, and only 3 of 17 (18%) who had liver biopsies approximately 20 years after exposure had histologic signs of progressive liver disease.
- **Ethnic background:** Disease progression appears to be slower and changes in liver histology less severe in African-Americans (Sterling 2004).
- **HCV-specific cellular immune response:** The severity of liver injury is influenced by the cellular immune response to HCV-specific targets. Inflammatory responses are regulated by complex mechanisms and probably depend on genetic determinants such as HLA expression (Hraber 2007). Whether this determines progression of liver disease is not clear.
- **Alcohol intake:** Alcohol increases HCV replication, enhances the progression of chronic HCV, and accelerates liver injury (Gitto 2008). Even moderate amounts of alcohol appear to increase the risk of fibrosis. Accordingly, in alcoholic patients with cirrhosis and liver failure a high prevalence of anti-HCV antibodies has been described. Alcohol intake should be avoided in all patients with chronic hepatitis C. There is no clear amount of safe alcohol intake.
- **Daily use of marijuana:** Daily use of marijuana has been associated with more rapid fibrosis progression, possibly through stimulation of endogenous hepatic cannabinoid receptors.
- **Other host factors:** Genetic polymorphisms of certain genes might influence the fibrosis progression rate (Jonsson 2008). For example, transforming growth factor B1 (TGF B1) phenotype and fibrosis stage are correlated. Patients with moderate to severe steatosis are at higher risk for developing hepatic fibrosis.
- **Viral coinfection:** Progression of hepatitis C clearly is accelerated in HIV-infected patients (see section on coinfection). Acute hepatitis B in a patient with chronic hepatitis C may be more severe. Chronic hepatitis B may be associated with decreased HCV replication as opposed to HCV monoinfected patients, al-

though HCV usually predominates. Nevertheless, liver damage is usually worse and progression faster in patients with dual HBV/HCV infections. Around one third of patients coinfecting with HBV and HCV lack markers of HBV infection (i.e., HBsAg) although HBV DNA is detectable.

- **Geography and environmental factors:** There are some obvious geographic differences (Lim 2008). For example, hepatocellular carcinoma is observed more often in Japan than in the United States. The reason for this phenomenon is not clear.
- **Use of steroids:** It is well known that use of steroids increases the HCV viral load, while the effect on aminotransferases is variable. They tend to decrease in most patients, although increases in transaminases and bilirubin have also been described. Reducing dosage of corticosteroids returns HCV viral load to baseline. However, the clinical consequences of corticosteroid use are largely unknown. It seems to be reasonable to assume that short-term use of corticosteroids is not associated with significant changes in long-term prognosis.
- **Viral factors:** The influence of viral factors on disease progression is unclear. Overall, there seems to be no significant role of different genotypes and quasi-species on fibrosis progression or outcome. However, coinfection with several genotypes may have a worse outcome as compared to mono-infection.

It is very difficult to predict the individual course of hepatitis C due to the many factors influencing disease progression. Today, liver biopsy is the best predictor of disease progression (Gebo 2002). The grade of inflammation and stage of fibrosis are useful in predicting further clinical course. In patients with severe inflammation or bridging fibrosis virtually all patients will develop cirrhosis within ten years. In contrast, patients with mild inflammation and no fibrosis have an annual progression risk to cirrhosis of around 1%.

Parameter	Points assigned		
	1	2	3
Ascites	Absent	Slight	Moderate
Bilirubin, mg/dL	<2	2-3	>3
Albumin, g/dL	>3.5	2.8-3.5	<2.8
Prothrombin time			
Seconds over control	<4	4-6	>6
INR	<1.7	1.7-2.3	>2.3
Encephalopathy	None	Grade 1-2	Grade 3-4

Table 1. Child-Pugh classification of severity of liver disease (Child 1964).

A total score of 5-6 is considered stage A (well-compensated disease); 7-9 is stage B (significant functional compromise); and 10-15 is stage C (decompensated disease). These grades correlate with one- and two-year patient survival: stage A - 100 and 85 percent; stage B - 80 and 60 percent; and stage C - 45 and 35 percent.

Several predictive models of disease progression that include clinical parameters (e.g., hepatic decompensation) and laboratory parameters (e.g., bilirubin, INR) have been evaluated, but none of these models is routinely used in the clinic at present. In patients with cirrhosis, the MELD score (Model for End-Stage Liver Disease) and the CHILD score (Table 1) are used to stage disease and to describe the prognosis in the near future (see Chapters 22 & 23). The MELD Score is used especially to estimate relative disease severity and likely survival of patients awaiting liver transplant. It is calculated as: $\text{MELD Score} = 10 \times ((0.957 \times \ln(\text{creatinine})) + (0.378 \times \ln(\text{bilirubin})) + (1.12 \times \ln(\text{INR}))) + 6.43$. An online calculator and further information can be found at the website of The United Network for Organ Sharing (UNOS) (<http://www.unos.org>).

Extrahepatic manifestations

Around 30 to 40% of patients with chronic hepatitis C have an extrahepatic manifestation of HCV (Zignego 2008). There is a wide variety of extrahepatic manifestations described as being associated with HCV:

- Hematologic manifestations (essential mixed cryoglobulinemia, lymphoma)
- Autoimmune disorders (thyroiditis, presence of various autoantibodies)
- Renal disease (membranoproliferative glomerulonephritis)
- Dermatologic disease (porphyria cutanea tarda, lichen planus)
- Diabetes mellitus

For further details refer to Chapter 16.

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