

HEPATITIS C

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History

In the mid 1970s it was shown that most of the post-transfusion cases of hepatitis were not due to hepatitis A or B. For the next decade, these cases were thought to be caused by a virus called Non-A Non-B Hepatitis virus. It was only in 1987 that the new virus was discovered by using a novel molecular cloning approach to identify the unknown organism. It was named hepatitis C virus. In 1990, blood banks began screening blood donors for hepatitis C, but it wasn't until 1992 that a blood test was perfected that effectively eliminated HCV from the blood transfusion supply

Epidemiology

Hepatitis C disease is a disease of the liver caused by the hepatitis C virus (HCV). The virus is a single strand RNA virus with an envelope included in the Flavivirus family. As with most RNA viruses, it is error-prone during replication of the nucleic acid chain and therefore shows large variability.

Disease burden in Louisiana: Hepatitis C virus (HCV) infection is the most common chronic bloodborne infection in the United States and Louisiana. According to the Center for Disease Prevention and Control (CDC) estimates during the 1980s, an average of 4,000 new infections occurred each year in Louisiana. However, since 1989 the annual number of new infections has declined by more than 80%, from 500 to 600 new (acute) infections each year. The number of acute cases reported however, is about 200 to 300 per year, about one third to one half of the actual number of cases.

According to the CDC, it is estimated that 80,000 residents of Louisiana are infected by the hepatitis C virus. Annually, 120 Louisiana residents are expected to die from hepatitis C. About 4,000 (5% of those infected by hepatitis C) are candidates for a liver transplant, at a cost of \$300,000 per transplant.

HCV is mostly spread by contact with blood and body fluids.

The hepatitis C virus circulates at low titers in the blood for a long time thus explaining why it is mostly spread by parenteral route (blood transfusion, intravenous drug abuse, nosocomial transmission in hospital with poor infection control standards). Before 1990, the risk of acquiring HCV from a blood transfusion was substantial (approximately 10%). Blood donor screening for antibodies to HCV (anti-HCV) with first-generation enzyme immunoassays began in 1990, succeeded by second- and third-generation tests in 1992 and 1996, respectively. Now that anti-HCV antibody can be detected easily, the current risk of acquiring chronic HCV infection from a blood transfusion is estimated at 0.01% to 0.001% per unit transfused (approximately one in 103,000 units).

Injectable drug use is a major risk factor. Injecting-drug use consistently has accounted for a substantial proportion of HCV infections and currently accounts for 60% of HCV transmission in the United States. A high proportion of infections continue to be associated with injecting-drug use, but for reasons that are

unclear, the dramatic decline in incidence of acute hepatitis C since 1989 correlates with a decrease in cases among injecting-drug users.

Nosocomial transmission of HCV is possible if infection-control techniques or disinfection procedures are inadequate, and contaminated equipment is shared among patients. Such transmission has rarely been reported in the United States, other than in chronic hemodialysis settings. Health-care, emergency medical (e.g. emergency medical technicians and paramedics), and public safety workers (e.g. fire-service, law-enforcement, and correctional facility personnel) who have exposure to blood in the workplace are at risk for being infected with bloodborne pathogens. However, prevalence of HCV infection among health-care workers, including orthopedic, general and oral surgeons, is no greater than the general population, averaging 1% to 2%, and is ten times lower than that for HBV infection. In a single study that evaluated risk factors for infection, a history of unintentional needle-stick injury was the only occupational risk factor independently associated with HCV infection. The average incidence of anti-HCV seroconversion after unintentional needle sticks or sharps exposures from an HCV-positive source is 1.8% (range: 0%-7%), with one study reporting that transmission occurred only from hollow-bore needles compared with other sharps.

The risk for HCV transmission from an infected health-care worker to patients appears to be very low. One published report exists of such transmission during performance of exposure-prone invasive procedures: HCV transmission was described from a cardiothoracic surgeon to five patients. Although factors (e.g. virus titer) might be related to transmission of HCV, no methods exist currently that can reliably determine infectivity, nor do data exist to determine threshold concentration of virus required for transmission.

The risk of sexual transmission of HCV appears to be minimal. Although the available data suggest that transmission can occur, the risk appears to be very small and is much less than it is for other common blood-borne infections, such as hepatitis B and HIV. The rate of transmission among discordant couples who are not using condoms is so low that HCV-positive patients who are in a mutually monogamous relationship can be reassured that they do not need to change their sexual practices, although their partners should be encouraged to be tested for HCV.

Transmission from mother to newborn is rare: Studies of infants born to HCV positive mothers show a seroconversion rate of 6%. The transmission rate seems to be related to the viral titer in the blood. Infants of mothers with more than 1,000,000 virions/ml had an infection rate of 36%. Coinfection with HIV leads to a higher transmission rate (15%).

Household contact: Case-control studies also have reported an association between nonsexual household contacts and acquiring hepatitis C. The presumed mechanism of transmission is direct or inapparent percutaneous or permucosal exposure to infectious blood or body fluids containing blood.

Other transmission: It appears that HCV is not very resistant and is rapidly degraded in the environment. In other countries, HCV infection has been associated with folk medicine practices, tattooing, body piercing and commercial barbering. However, in the United States, case-control studies have reported no association between HCV infection and these types of exposures.

HCV in the environment: Little is known about the environmental survival of HCV except that its RNA in plasma or serum has been found to be stable at 4° C for seven days. Unlike HIV, **the current assumption is that hepatitis C virus can live for a long time outside the body (estimates vary between seven to ten days, to weeks or months)**. For example, wiping blood off a razor or nail clippers won't kill it. Dried blood could still cause transmission of hepatitis C. Hand contact with blood-contaminated surfaces such as laboratory benches, test tubes, or laboratory instruments may transfer the virus to skin or mucous membranes.

Exposures in the U.S.: Recent studies have demonstrated that injecting-drug use currently accounts for 60% of HCV transmission in the United States. Although the role of sexual activity in transmission of HCV remains unclear, less than or equal to 20% of persons with HCV infection report sexual exposures (i.e. exposure to an infected sexual partner or to multiple partners) in the absence of percutaneous risk factors. Other known exposures (occupational, hemodialysis, household, perinatal), together account for approximately 10% of infections. Thus, a potential risk factor can be identified for approximately 90% of persons with HCV infection. In the remaining 10%, no recognized source of infection can be identified, although most persons in this category are associated with a low socioeconomic level. Although a low socioeconomic level has been associated with several infectious diseases and might be a surrogate for high-risk exposures, its nonspecific nature makes targeting prevention measures difficult.

Disease burden: A study by the CDC suggests that 4.1 million individuals in the U.S. have been infected with hepatitis C virus (HCV), and most have chronic infections. More than 15,000 participants in the National Health and Nutrition Examination Survey conducted between 1999 and 2002 provided medical histories and were tested for antibodies to HCV, the presence of HCV RNA and serum alanine aminotransferase levels (ALT, a measure of liver function). The prevalence of antibodies to HCV was 1.6%; peak prevalence (4.3%) was observed among individuals aged 40 to 49 years. Almost half of those with antibodies to HCV who were aged 20 to 59 years reported a history of injection drug use. Three characteristics - abnormal serum ALT level, any history of injection drug use and history of blood transfusion before 1992 - identified 85.1% of HCV RNA–positive participants aged 20 to 59 years.

The incubation period varies from two weeks to six months (mean - eight weeks).

Clinical Description

After initial exposure, HCV RNA can be detected in the blood in one to three weeks. Within an average of 30 days (15-150 days), virtually all patients develop a liver cell injury as shown by an elevation of serum ALT (formerly SGPT).

The majority of the liver cell injury stage is asymptomatic. Only 25% to 35% develop malaise, weakness, anorexia and some become icteric. Anti HCV can be detected in 50% to 70% of patients at the onset of symptoms and in 90% of patients three months after infection.

Complete recovery: HCV infection is self limited in only 15% to 25% of cases. Recovery is characterized by disappearance of HCV RNA from the blood and the return of liver enzymes to normal.

A few cases (about 1%) develop fulminant hepatitis.

Chronic HCV Infection develops in most persons (75%-85%), with persistent or fluctuating ALT elevations indicating active liver disease developing in 60% to 70% of chronically infected persons. In the remaining 30% to 40% of chronically infected persons, ALT levels are normal. No clinical or epidemiologic features among patients with acute infection have been found to be predictive of either persistent infection or chronic liver disease. Moreover, various ALT patterns have been observed in these patients during follow-up, and patients might have prolonged periods (≥ 12 months) of normal ALT activity even though they have histologically-confirmed chronic hepatitis. Thus, a single ALT determination cannot be used to exclude ongoing hepatic injury, and long-term follow-up of patients with HCV infection is required to determine their clinical outcome or prognosis. The course of chronic liver disease is usually insidious, progressing at a slow rate without symptoms or physical signs in the majority of patients during the first two or more decades after infection. Frequently, chronic hepatitis C is not recognized until asymptomatic persons are identified as HCV-positive during blood-donor screening, or elevated ALT levels are detected during routine physical examinations.

Most studies have reported that cirrhosis develops in 10% to 20% of persons with chronic hepatitis C over a period of 20 to 30 years, and hepato-cellular carcinoma (HCC) develops in 1% to 5%.

Although factors predicting severity of liver disease have not been well-defined, recent data indicate that increased alcohol intake, being aged older than 40 years at infection and being male are associated with more severe liver disease. Even intake of moderate amounts (>10 g/day) of alcohol in patients with chronic hepatitis C might enhance disease progression. Persons who have chronic liver disease are at increased risk for fulminant hepatitis.

Extrahepatic manifestations of chronic HCV infection are considered to be of immunologic origin and include cryoglobulinemia, membranoproliferative glomerulonephritis and porphyria cutanea tarda.

Laboratory Tests

Serologic Assays

The tests most often used for the diagnosis of HCV infection are those that measure antibodies to HCV. These tests detect anti-HCV in 97% of infected patients, but do not distinguish between acute, chronic, or resolved infection. As with any screening test, positive predictive value of enzyme immunoassay (EIA) for anti-HCV varies depending on prevalence of infection in the population and is low in populations with an HCV-infection prevalence of less than 10%.

Recombinant ImmunoBlot Assays (RIBA) use the same antigens as EIA but in an immunoblot format. Supplemental testing with a more specific assay such as RIBA of a specimen with a positive EIA result prevents reporting of false-positive results, particularly in settings where asymptomatic persons are being tested. Supplemental test results might be reported as positive, negative, or indeterminate.

An anti-HCV-positive person is defined as one whose serologic results are EIA-test-positive and supplemental-test-positive. Persons with a negative EIA test result or a positive EIA and a negative supplemental test result are considered uninfected, unless other evidence exists to indicate HCV infection (e.g. abnormal ALT levels in immuno-compromised persons or persons with no other etiology for their liver disease). Indeterminate supplemental test results have been observed in recently infected persons who are in the process of seroconversion, as well as in persons chronically infected with HCV. Indeterminate anti-HCV results also might indicate a false-positive result, particularly in those persons at low risk for HCV infection.

Nucleic Acid Detection

The diagnosis of HCV infection also can be made by qualitatively detecting HCV RNA using gene amplification techniques (e.g. RT-PCR). HCV RNA can be detected in serum or plasma within one to two weeks after exposure to the virus and weeks before the onset of ALT elevations or the appearance of anti-HCV. Rarely, detection of HCV RNA might be the only evidence of HCV infection. Although not FDA-approved, RT-PCR assays for HCV infection are used commonly in clinical practice. Most RT-PCR assays have a lower limit of detection of 100 to 1,000 viral genome copies per mL. With adequate optimization of RT-PCR assays, 75% to 85% of persons who are anti-HCV- positive and greater than 95% of persons with acute or chronic hepatitis C will test positive for HCV RNA. Some HCV-infected persons might be only intermittently HCV RNA-positive, particularly those with acute hepatitis C or with endstage liver disease caused by hepatitis C. To minimize false-negative results, serum must be separated from cellular components within two to four hours after collection and preferably stored frozen at -20°C to -70°C. If shipping is required, frozen samples should be protected from thawing. Because of assay variability, rigorous quality assurance and control should be in place in clinical laboratories performing this assay, and proficiency testing is recommended.

Surveillance

Hepatitis C acute infection and past infection are both reportable.

Case Definition

All cases having a positive hepatitis C result (EIA, RIBA, quantitative RT-PCR) will be entered in the surveillance database in one of two categories:

1-Acute Hepatitis C

Clinical case definition: An acute illness with discrete onset of symptoms and jaundice or elevated serum aminotransferase levels: AST \geq 280 and AL T \geq 350

Laboratory confirmation:

- 1- IgM antiHAV negative and
- 2- IgM antiHBc negative (if done) or HBsAg negative and
- 3- Antibody to hepatitis C virus (antiHCV) positive, or RT-PCR or any other test showing viral presence

Confirmed: A case that meets the clinical case definition and is lab confirmed

Probable: A case that meets the clinical case definition and is antiHCV screening test positive and has not been verified by an additional more specific assay or signal to cutoff assay is unknown and anti-HAV IgM unknown and anti-Hbcore IgM unknown and HbsAg unknown.

2-Hepatitis C Past or present infection

Clinical case definition: Most cases are asymptomatic

Laboratory confirmation: EIA positive with signal to cut off ratio \geq 3.8, RIBA, quantitative RT-PCR, any nucleic acid positive test

Confirmed: A case that meets the lab case definition

Probable: antiHCV EIA positive with ALT above normal

Suspect: antiHCV EIA positive only

Treatment

Who should get HCV treatment and when

The The AASLD and IDSA HCV Guidance Panel recommends antiviral treatment for anyone diagnosed with chronic HCV infection, with the exception of people with limited life expectancy due to “non-hepatic causes.” If resources are limited for the patient to get treatment, the panel deems it “most appropriate to treat those at greatest risk of disease complications before treating those with less advanced disease,” according to the guidelines. To determine those at greatest risk for complications, the panel recommends noninvasive testing or liver biopsy for assessing hepatic fibrosis stage, which determines the urgency for treatment.

Initial treatment of HCV

Treatment-naive patients with HCV and different genotypes have posed a challenge. Some of the treatment recommendations from the panel for the various genotypes are: for treatment-naive patients with HCV genotype 1a, the panel recommends a daily fixed-dose combination of Harvoni (ledipasvir/sofosbuvir, Gilead Sciences) for 12 weeks, a daily fixed-dose combination of Viekira Pak (paritaprevir/ritonavir/ombitasvir/dasabuvir, AbbVie) and weight-based ribavirin (RBV) for 12 weeks in patients without cirrhosis or 24 weeks in patients with cirrhosis, among other treatments. For treatment-naive patients with HCV genotype 2, the panel recommends a daily regimen of Sovaldi (sofosbuvir, Gilead Sciences) and weight-based RBV for 12 weeks. For patients with HCV genotype 3, the panel recommends a daily sofosbuvir and weight-based RBV plus weekly pegylated-interferon (PEG-IFN) for 12 weeks for patients eligible to take PEG-IFN. For patients unable to take PEG-IFN, a daily sofosbuvir and weight-based RBV regimen for 24 weeks is recommended. See the list of guidelines for other genotypes and treatment recommendations.

Prevention

The AASLD and IDSA HCV Guidance Panel has released updated guidelines for the treatment of hepatitis C virus infection. For screening, it recommends behaviors and conditions that may increase risk for contracting HCV. Every person that is recommended for HCV testing should be tested for anti-HCV using an FDA-approved test, according to the researchers, with positive results being confirmed through nucleic acid testing for HCV RNA. The panel also recommends annual testing be performed on men who have sex with men and people who inject drugs, as these populations are at increased risk.

Screening for chronic HCV infection

Anyone with an ALT level that is elevated above normal or with a history of risk factors, such as injection drug use, blood transfusion before July 1992, treatment with clotting factor concentrate before 1987, or long-term hemodialysis, should be screened for chronic HCV infection by testing for the presence of antibody to HCV.

Blood, organ, semen donor screening: The efficacy of blood donor screening program depends on the sensitivity of the screening test. With newer anti-HCV screening tests and combination with serum ALT level assessment, the detection of HCV infection has greatly improved.

Hemophiliacs: Heating the factor VIII at 80°C for 72 hours prevents the risk of transmission of HCV.

Blood and body fluid exposure of Health Care Workers (HCW): In case of exposure of HCWs to blood or body fluids, the National Hepatitis Detection and Treatment Program recommends testing source patients for ALT. If the source patient is unknown or if the source is anti-HCV positive or has elevated AST, then the exposed HCW should have a baseline serum ALT and anti-HCV. If initially negative, anti-HCV should be repeated at three and six months.

Recommendations regarding post-exposure administration of Immune Globulin are controversial since study results have not conclusively proven its beneficial effect. Since the beginning of HCV testing, those with antibodies have been rejected as plasma donors. Therefore it is doubtful if immunoglobulin contains antibodies to HCV in sufficient concentration to be effective.

Decontamination of HCV in the environment

In vitro studies have shown that bleach is effective for inactivating many pathogens, including HIV and hepatitis B. However, relatively little is known about the inactivation of HCV by chemical germicides. The lack of an in-vitro cultivation system for HCV limits the ability to investigate the efficacy of disinfection. Published information comes mainly from experiments in which the integrity of viral

particles, antigens, nucleic acid and/or enzymes is used as a measure of the presence or absence of infectious virus. Such tests may show viral presence, but do not necessarily answer questions of infectivity. Even polymerase chain reaction (PCR) detection methods cannot distinguish between infectious and inactivated virus. To address this challenge, some researchers have turned to animal models. Unfortunately, the only truly appropriate animal model is the chimpanzee. Given their endangered status, chimpanzee studies are both ethically difficult and very expensive. More recently, other viruses including the bovine diarrhea virus (BVDV) have been used as surrogates for HCV.

The current challenge of determining true infectivity limits our ability to evaluate appropriate dilution and exposure times. **A 1:10 dilution of domestic bleach is commonly recommended for clean-up of blood spills. This concentration should be adequate to deal with HCV (and HBV) in blood,** although supportive evidence is lacking.

As with any disinfectant, there are factors that reduce bleach's effectiveness against HCV. These include the amount of organic material, e.g., fresh, dried or clotted blood, left in or on the equipment ('soil load'), how long the blood has been sitting, the length of time bleach is in contact with the equipment, the "freshness" of the bleach and whether or not the bleach is used properly.