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Hepatitis C

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What is hepatitis C?

Hepatitis C is an infection of the liver caused by the hepatitis C virus (HCV). It is difficult for the human immune system to eliminate the virus from the body, and infection with HCV usually becomes chronic. Over decades, chronic infection with HCV damages the liver and can cause liver failure in some people. In the U.S., the number of new cases of infection with HCV has declined over the last 10 years from a peak of some 200,000 annually to about 19,000 in 2006. When the virus first enters the body, there usually are no symptoms, so these numbers are estimates. Up to 85% of newly infected people fail to clear the virus and become chronically infected. In the U.S., more than three million people are chronically infected with HCV. Infection is most common among people who are 40 to 60 years of age, reflecting the high rates of infection in the 1970s and 1980s. There are 8,000 to 10,000 deaths each year in the U.S. related to HCV. HCV is the leading cause of liver transplantation in the U.S and is a risk factor for liver cancer.

What is the nature (biology) of the hepatitis C virus?

'Hepatitis' means inflammation of the liver. HCV is one of several viruses that can cause hepatitis. It is unrelated to the other common hepatitis viruses (for example, hepatitis A or hepatitis B). HCV is a member of the *Flaviviridae* family of viruses. Other members of this family of viruses include those that cause yellow fever and dengue.

Viruses belonging to this family all have ribonucleic acid (RNA) as their genetic material. All hepatitis C viruses are made up of an outer coat (envelope) and contain enzymes and proteins that allow the virus to reproduce within the cells of the body, in particular, the cells of the liver. Although this basic structure is common to all hepatitis C viruses, there are at least six distinctly different strains of the virus which have different genetic profiles (genotypes). In the U. S., genotype 1 is the most common form of HCV. Even within a single genotype there may be some variations (genotype 1a and 1b, for example). Genotyping is important to guide treatment because some viral genotypes respond better to therapy than others. The genetic diversity of HCV is one reason that it has been difficult to develop an effective vaccine since the vaccine must generate viral proteins from each genotype.

How does liver damage occur in hepatitis C infection?

The presence of HCV in the liver triggers the human immune system, which leads to inflammation. Over time (usually decades), prolonged inflammation may cause scarring. Extensive scarring in the liver is called cirrhosis. When the liver becomes cirrhotic, the liver fails to perform its normal functions, (liver failure), and this leads to serious complications and even death. Cirrhotic livers also are more prone to become cancerous.

How is hepatitis C virus spread and how can transmission be prevented?

HCV is spread (transmitted) most efficiently through inadvertent exposure to infected blood.

The most common route of transmission is needles shared among users of illicit drugs.

Accidental needle-sticks in healthcare workers also have transmitted the virus.

The average risk of getting HCV from a stick with a contaminated needle is 1.8% (range 0% to 10%).

Prior to 1992, some people acquired the infection from transfusions of blood or blood products. Since 1992, all blood products are screened for HCV, and cases of HCV due to blood transfusion now are extremely rare.

HCV also can be passed from mother to unborn child. Approximately 4 of every 100 infants born to HCV-infected mothers become infected with the virus.

A small number of cases are transmitted through sexual intercourse. The risk of transmission of HCV from an infected individual to a non-infected spouse or partner without the use of condoms over a lifetime has been estimated to be 1% to 4%

Finally, there have been some outbreaks of HCV when instruments or sharp tool have been re-used without appropriate cleaning between patients.

Transmission of HCV can be prevented in several ways.

Programs have been aimed at avoiding needle sharing among drug addicts. Needle exchange programs and educational interventions have reduced high-risk behaviors. However, the population of drug addicts is a difficult population to reach, and rates of HCV remain high among addicts (30% of younger users).

Among healthcare workers, safe needle-usage techniques have been developed to reduce accidental needle-sticks. Newer syringes have self-capping needle systems that avoid the need to manually replace a cap after drawing blood and reduce the risk of needle-sticks.

There is no clear way to prevent transmission of the HCV from mother to child.

Persons with multiple sexual partners should use barrier precautions such as condoms to limit the risk of HCV as well as other sexually-transmitted diseases.

Monogamous couples should consider the low risk of transmission when deciding whether to use condoms during intercourse. Some couples may decide to use them and some may not.

Screening tests for blood products have almost eliminated the risk of transmission through transfusion, estimated by the CDC to be less than one in two million transfused blood products.

People with HCV should not share razors or toothbrushes with others.

It is critical that physicians and clinics follow manufacturer's directions for sterilizing/cleaning instruments and that disposable sharp instruments be discarded properly.

It is important to realize that HCV is not spread by casual contact. Thus, shaking hands, kissing, and hugging are not behaviors that increase the risk of transmission. There is no need to use special isolation procedures when dealing with infected patients.

What are the symptoms of hepatitis C infection?

About 75% of people have no symptoms when they first acquire HCV infection. The remaining 25% may complain of fatigue, loss of appetite, muscle aches or fever. Yellowing of the skin or eyes (jaundice) is rare at this early stage of infection.

Over time, the liver in people with chronic infection may begin to experience the effects of the persistent inflammation caused by the immune reaction to the virus. Blood tests may show elevated levels of liver enzymes, a sign of liver damage, which is often the first suggestion that the infection may be present. Patients may become easily fatigued or complain of nonspecific symptoms.

As cirrhosis develops, symptoms increase and may include :

weakness,

loss of appetite,

weight loss,

breast enlargement in men,

a rash on the palms,

difficulty with the clotting of blood, and

spider-like blood vessels on the skin.

In patients with advanced cirrhosis, the liver begins to fail. This is a life-threatening problem. Confusion and even coma (encephalopathy) may result from the inability of the liver to process certain toxic substances.

Increased pressure in the blood vessels of the liver (portal hypertension) may cause fluid to build up in the abdominal cavity (ascites) and result in engorged veins in the swallowing tube (esophageal varices) that tear easily and can bleed suddenly and massively. Portal hypertension also can cause kidney failure or an enlarged spleen resulting in a decrease of blood cells and the development of anemia, increased risk of infection and bleeding.

In advanced cirrhosis, liver failure causes decreased production of clotting factors. Patients with advanced cirrhosis often develop jaundice because the damaged liver is unable to eliminate a yellow compound, called bilirubin that is formed from the hemoglobin of old red blood cells.

What conditions outside the liver are associated with hepatitis C?

Most of the signs and symptoms of HCV relate to the liver. Less commonly, HCV causes conditions outside of the liver.

An example is when the body produces unusual antibodies called 'cryoglobulins'. These cryoglobulins cause inflammation of the arteries (vasculitis) which may damage the skin, joints, and kidneys. Patients with cryoglobulinemia may have joint pain, arthritis, a raised purple rash on the legs, generalized pain or swelling. In addition, these patients may develop Raynaud's phenomenon, in which the fingers and toes turn color (white, then purple, then red) and become painful at cold temperatures.

Two skin conditions, lichen planus and porphyria cutanea tarda, have been associated with chronic infection with HCV.

For reasons that are unclear, diabetes is three times more common among patients with chronic HCV infection than in the general population.

Low platelet counts may occur as a result of antibody-mediated platelet destruction.

HCV also is associated with B-cell lymphoma, a cancer of the lymph system.

What is the usual progression of chronic infection with the hepatitis C virus?

Our understanding of the natural progression (history) of HCV infection still is evolving.

Of 100 people infected with HCV, it is estimated that 75 to 85 will become chronically infected, 60 to 70 will develop liver disease, 5 to 20 will develop cirrhosis and 1 to 5 will die from complications of liver disease like cirrhosis or liver cancer.

Scientists are learning more about what causes some people to have milder problems and others to have serious complications. Drinking alcohol or acquiring other hepatitis viruses are risk factors for severe disease. Thus, persons who have chronic hepatitis C should avoid drinking and should be vaccinated against the other hepatitis viruses (A and B).

Liver cancer (hepatocellular carcinoma) is associated with cirrhosis due to chronic HCV infection. Some experts recommend screening patients with HCV and cirrhosis for liver cancer every six months with abdominal ultrasound and a blood test for alpha-fetoprotein (a marker for liver cancer). The effectiveness of this screening is unclear.

Who is at high risk and should be tested for hepatitis C infection?

Currently, screening for HCV is not recommended as part of a routine physical examination.

Rather, testing should be done in individuals at high risk for infection including current and past users of injectable drugs and persons exposed to infected blood or organs from infected persons.

Children born to chronically infected mothers should be tested to determine if they carry the virus.

Persons with abnormal levels of liver enzymes in the blood also should be tested.

These are not the only circumstances under which tests may be done. In general, testing is recommended when exposure to the virus is suspected.

What are the diagnostic tests for hepatitis C virus and how are they used to diagnose hepatitis C virus infection?

Several diagnostic tests currently are available for the diagnosis of HCV. They can be categorized according to the way the tests are used.

Screening tests

Screening tests are tests that are used to diagnose a condition or disease among individuals not known to have the disease. It is particularly useful for individuals who have risk factors for the condition or disease. The first step in screening for HCV is to test blood for the antibody to HCV using an enzyme-linked immunosorbent assay (ELISA). If the ELISA test is negative (does not find the antibody), the patient is assumed to be free of HCV. It takes several weeks (up to six months) for antibodies to develop after the initial infection with HCV, so this screening test may miss a few newly-infected individuals. However, in HCV physicians usually are looking for chronic infection so missing a few recently-infected individuals is not of much importance.

The ELISA test for HCV antibody is not perfect and may sometimes be positive in people who are not currently infected. Thus, if the ELISA test for HCV antibody is positive, additional testing is done to confirm the diagnosis with another type of test for the antibody. One such test is called the recombinant immunoblot assay (RIBA). It is read as either 'positive', 'negative' or 'indeterminate'. Indeterminate means that the result is unclear. Another option is to use molecular tests to measure the amount of HCV ribonucleic acid (RNA) in the blood (see below).

Molecular tests for hepatitis C virus

As previously described, HCV is an RNA virus, meaning that it contains RNA. Several tests (assays) are available to measure the amount of HCV RNA in a person's blood. These tests are referred to as molecular tests because they examine the virus at the molecular level. A single negative test for RNA does not mean that there is no infection because the virus may appear in the blood intermittently or may exist in small amounts. Newer tests have helped by detecting smaller and smaller amounts of virus in the blood.

Testing for RNA is useful in determining whether or not a patient has circulating virus in the blood (viremia). Hence, it can be used to confirm that a positive ELISA truly reflects active hepatitis C virus infection.

RNA testing also should be done in individuals who may have been recently exposed to HCV. HCV RNA testing is more sensitive (that is, will detect more cases) than the conventional ELISA testing in this setting. The reason for this greater sensitivity is that it may take a person several weeks after exposure to HCV to develop the antibodies, whereas HCV RNA becomes detectable one to three weeks after exposure. Finally, HCV RNA testing may be helpful to assess a patient's virologic response to treatment at certain time points during antiviral therapy (see treatment of HCV below).

How are the results of the hepatitis C virus tests interpreted?

The table below provides guidelines for interpreting the results of testing for anti-hepatitis C virus by ELISA and RIBA and for hepatitis C virus RNA. These are standard interpretations, but it is important to remember that the diagnosis of hepatitis C should be made by an experienced clinician who is familiar with the patient's medical history.

Anti-HCV (ELISA)	Anti-HCV (RIBA)	HCV RNA	Interpretation
Negative	Negative	Negative	No infection
Positive	Positive	Positive	Ongoing infection
Positive	Positive	Negative	Past or current infection. Additional or repeat testing should be done to exclude fluctuating or low levels of viremia.
Positive	Negative	Positive	False positive ELISA; no infection
Positive	Indeterminate	Negative	Situation unclear, consider additional testing
Negative	Negative	Positive	New (acute) HCV infection or chronic HCV infection in an immunocompromised person unable to make adequate antibodies.

What tests identify the virus genotypes?

Blood tests have been developed to identify the HCV genotype. This information is used to help guide treatment.

What is the role of a liver biopsy in the management of chronic hepatitis C?

Blood tests can tell the clinician whether HCV is present but cannot tell the level of liver damage that has occurred. Liver biopsy allows the clinician to determine how much inflammation and scarring is present in a small sample of liver tissue. Liver biopsy may be recommended when the clinician is uncertain about whether to begin treatment or wishes to monitor the response within the liver to therapy.

Who should receive antiviral therapy for hepatitis C virus?

Patients at risk for cirrhosis should be considered for treatment of HCV. According to a consensus statement from the National Institutes of Health (NIH) these include persons with:

HCV infection and persistent elevation of ALT (alanine aminotransferase, a liver enzyme in the blood)

High levels of HCV RNA in the blood

HCV infection and evidence of fibrosis (scarring) on liver biopsy

HCV infection and evidence of at least moderate inflammation and liver cell injury (necrosis) on liver biopsy

These are general guidelines. Patients and providers may decide that treatment is needed for other reasons. For example, patients with HIV have a more rapid course of liver injury and may need treatment at an earlier stage. Newer therapies may be offered to selected patients in research settings.

Individuals who should not be treated with antiviral therapy include those who are unable to comply with the treatment schedule, should not take the specific medications (for example, allergy), and have reversible serious untreated conditions such as unstable heart disease, uncontrolled high blood pressure, or untreated major depression.

Patients with unstable (decompensated) cirrhosis are at high risk for complications for treatment and usually do not receive medical treatment, except in research settings. Fundamentally, the decision regarding antiviral therapy in chronic HCV infection should be tailored to the individual patient with careful consideration of the risks and benefits.

All patients with HCV should be vaccinated against hepatitis B and hepatitis A. They also should be counseled on measures to prevent the spread of HCV and eliminating alcohol use. Finally, risk behaviors for HCV overlap with those of HIV, and all patients with HCV should be tested for HIV.

What are the different patterns of response to antiviral treatment?

Treatment responses are mainly defined by results of the HCV RNA testing. Four patterns of response to antiviral treatment have been described:

1. sustained virologic response,
2. relapse,
3. partial response, and
4. non-response.

Sustained virologic response

The optimal response is a sustained virologic response (SVR), defined as the absence of detectable HCV RNA in serum using a sensitive test at the end of the treatment and six months later. Most of these individuals will remain in remission (no signs of the disease) indefinitely, with no detectable hepatitis C virus RNA in the blood or liver. Moreover, follow-up biopsies show a marked reduction in inflammation and there even can be regression of scarring. Longer follow-up of these patients is necessary, however, to evaluate definitively whether sustained responders will avoid the complications of cirrhosis and live longer.

Relapse

Relapsers are patients who initially eliminate the RNA from their blood but then develop detectable RNA again shortly after discontinuing therapy. The RNA becomes detectable again within six months and usually within the first three months of stopping treatment.

Partial responders

Patients whose HCV RNA levels decline but never become undetectable are referred to as partial responders.

No response

Patients who have sustained levels of detectable HCV RNA during therapy are known as non-responders. Patients in whom HCV RNA becomes undetectable during the early period of treatment but reappears before the end of therapy, should probably likewise be considered non-responders. This reappearance of HCV RNA during therapy is referred to as a 'break through' of HCV.

What are the goals of therapy for hepatitis C virus?

The ultimate goals of antiviral therapy are to eliminate HCV, improve or normalize the liver tests and histology (microscopic appearance), prevent progression to cirrhosis and liver cancer, prolong survival, and improve the quality of life.

As already indicated, only a sustained virologic response provides the possibility of achieving all of the ultimate goals, since most patients who have an SVR will remain in remission indefinitely. The rest of the patients (non-responders, partial responders and relapsers) may show improvement in blood tests with or without relief of symptoms.

What are the therapy options for previously untreated patients with chronic hepatitis C?

For previously untreated patients without reasons to be excluded from treatment, the optimal treatment is combined treatment with pegylated interferon and ribavirin (Rebetol, Copegus). Patients who have reasons not to receive ribavirin may be treated solely with pegylated interferon. Older preparations of interferon are less effective and less commonly used.

Pegylated interferon

Interferons are a family of naturally occurring proteins that are produced by the body to fight viral infections. To produce pegylated interferon, the interferon is processed by attaching ethylene glycol to it. This process is called pegylation and it slows the elimination of interferon from the body so that its effects are more prolonged. There are currently two types of pegylated interferon: pegylated interferon alpha 2b (Peg-Intron A) and pegylated interferon alpha 2a (Pegasys). Both pegylated interferon alpha 2b and 2a; are given as a subcutaneous injection once a week.

Optimally, pegylated interferon therapy should be combined with ribavirin. In persons who cannot take ribavirin, monotherapy with pegylated interferon may be used. Monotherapy has been shown to achieve sustained virologic response rates of 23% to 25% in patients.

Ribavirin

The antiviral agent, ribavirin (Rebetol, Copegus), is a nucleoside analogue that is taken by mouth. Nucleoside analogues are man-made molecules that closely resemble the biochemical units that make up genetic material (RNA and DNA). Ribavirin works by fooling the virus into using it instead of the normal building blocks, thereby slowing viral reproduction. Ribavirin has not worked well when used alone for hepatitis C.

Combined pegylated interferon and ribavirin

Combined therapy with both pegylated interferon and ribavirin produces a sustained virologic response in 28% to 50% of patients with genotype 1.

For unknown reasons, response rates are lower in African American persons and higher in Caucasians.

In patients with genotype 2, sustained response rates are higher (76% to 82%).

The duration of therapy depends on the genotype of the HCV.

Hence the recommended duration of treatment for HCV genotype 2 and 3 is 24 weeks and for genotype 1 is 48 weeks.

Sustained virologic response usually is accompanied by a return to normal serum ALT levels and improvement in inflammation within the liver.

Combination therapy is associated with more side effects than monotherapy (see below). In research studies, up to 20% of patients receiving combination therapy required a reduction in the doses or discontinuation of therapy because of the side effects. Nevertheless, combination therapy represents significant progress in the treatment of chronic HCV and is the current standard of care.

Some patients treated successfully with combination therapy still have detectable virus after 12 weeks of treatment but go on to have a sustained response. Therefore, patients on combination therapy should have hepatitis C virus RNA measured at 24 weeks of therapy. In those who are still positive for the virus at that time, consideration is given to stopping treatment, since the chance of sustained response is small.

How are relapses and nonresponders treated?

The optimal treatment for nonresponders and relapsers is not well established.

A minority of nonresponders (6% to 12%) will respond to a second course of pegylated interferon and ribavirin.

Patients initially treated with older interferon alpha monotherapy can be considered for the therapy of either pegylated interferon alpha monotherapy or pegylated interferon alpha plus ribavirin therapy.

Newer preparations of interferon such as 'consensus interferon' and albumin interferon are being studied and show promise in persons who did not respond to combination therapy.

Despite the failure to achieve sustained virologic response, treatment may slow the progression of HCV to cirrhosis, although this has not been shown for certain.

Should individuals with acute hepatitis C be treated?

When people first acquire HCV, the infection is said to be 'acute'. There is no standard approach to treatment for acute HCV. Most patients with acute HCV do not have symptoms, so they are not recognized as being infected. However, some have low-grade fever, fatigue or other symptoms that lead to an early diagnosis. Others who become infected have a known exposure to an infected source, such as a needlestick injury, and are monitored closely. Treatment decisions should be made on a case-by-case basis. However many experts prefer to hold treatment for several months to see whether the patient eliminates the virus without treatment.

What are the side effects of treatment for hepatitis C virus?

Flu-like symptoms, hair thinning and depression are common side effects of interferon or pegylated interferon. Depression may be serious and is common enough that patients should be monitored for this side effect.

Interferons may cause transient bone marrow suppression resulting in reduced white blood cell counts and hemoglobin. Reductions in white blood cell counts may cause increased susceptibility to infection. Death rarely occurs as a result of therapy, but may occur from progressive liver failure in patients with advanced cirrhosis.

Certain side effects are attributed to the addition of ribavirin to interferon, including nausea, cough, shortness of breath, rash, itching, insomnia, and loss of appetite.

Ribavirin also causes anemia due to the destruction of red blood cells (hemolysis). This anemia is usually mild but can become clinically significant. Ribavirin particularly may cause destruction of red blood cells (hemolysis) in people with kidney failure. Anemia improves with a reduction in the dose of ribavirin.

Ribavirin also accumulates in the testicles and ovaries and causes birth defects in animals. Although no birth defects have been reported in humans as yet, both men and women should use contraceptive measures to avoid pregnancy during and for at least six months after ribavirin treatment.

What about liver transplantation for hepatitis C?

HCV is the leading reason for liver transplantation in the U.S., accounting for 40% to 45% of transplants. HCV routinely recurs after transplantation and infects the new liver. Approximately 25% of these patients with recurrent hepatitis will develop cirrhosis within five

years of transplantation. Despite these findings of recurrence, the five-year survival rate for patients with HCV is comparable to that of patients who are transplanted for other types of liver disease.

Treatment for recurrent hepatitis is not a simple issue. Interferon is an immune modulator (modifier) that may promote rejection of the transplanted liver. Furthermore, interferon may not be well tolerated by patients who just underwent transplantation and are taking many different kinds of medications.

What is the current research and what is in the future for hepatitis C?

As our awareness of HCV infection increases, more and more patients are being diagnosed with this condition. Current research includes diagnosis, natural history, treatment, and vaccine development.

Diagnosis: More accurate tests are being developed to detect even smaller amounts of the virus.

Natural history: There is much we do not know about the natural history of chronic HCV. Why do some people clear the virus spontaneously? What makes some people develop cirrhosis when others appear to have little liver damage? What predicts response to treatment or re-treatment?

Treatment: New formulations of interferon are being developed in the hopes of improving response rates. In addition, new agents are being tested in combination with pegylated interferon and ribavirin. Some of these agents, like telaprevir, inhibit protease enzymes that HCV needs in order to reproduce.

Vaccine development: Scientists have not been able to develop an effective vaccine against HCV. This is partly due to the ability of the HCV to change (mutate) and evade the body's immune responses.

Hepatitis C at A Glance

HCV is one of several viruses that cause hepatitis (inflammation of the liver).

Up to 85% of individuals who are initially (acutely) infected with HCV will fail to eliminate the virus and will become chronically infected.

HCV is spread most commonly through inadvertent exposure to infected blood. Intravenous drug abuse is the most common mode of transmission. The risk of acquiring HCV through sexual contact is low.

Generally, patients do not develop symptoms of chronic infection with HCV until they have extensive scarring of the liver (cirrhosis). Some individuals, however, may have fatigue and other non-specific symptoms in the absence of cirrhosis. A minority of patients with HCV have symptoms from organs outside of the liver.

In the U.S., Infection with HCV is the most common cause of chronic hepatitis and the most common reason for liver transplantation.

HCV is diagnosed by determining levels in the blood of antibodies to the virus and then confirmed with other tests for viral RNA. The amount of viral RNA in the blood (viral load) does not correlate with the severity of the disease but can be used to track the response to treatment.

A liver biopsy may be used to assess the amount of liver damage (liver cell injury and scarring), which can be important in planning treatment.

Considerable progress has been made in the treatment of HCV. Combined therapy with pegylated interferon and ribavirin is the standard treatment regimen.

Treatment results in reduced inflammation and scarring of the liver in most sustained responders and also occasionally (and to a much lesser extent) in those who relapse or do not respond.