

Chronic Hepatitis C

The hepatitis C virus is one of the most important causes of chronic liver disease in the United States. Almost 4 million Americans or 1.8 percent of the U.S. population have an antibody to hepatitis C, indicating an ongoing or previous infection with the virus.

A distinct and major characteristic of hepatitis C is its tendency to cause chronic liver disease. At least 75 percent of patients with acute hepatitis C ultimately develop chronic hepatitis C infection, and most of these patients have accompanying chronic liver disease.

Chronic hepatitis C varies greatly in its course and outcome. At one end of the spectrum are patients who have no signs or symptoms of liver disease and completely normal levels of serum liver enzymes. Liver biopsy usually shows some degree of chronic hepatitis, but the degree of injury is usually mild, and the overall prognosis may be good. At the other end of the spectrum are patients with severe hepatitis C who have symptoms, hepatitis C virus RNA in the serum, and elevated serum liver enzymes, and who ultimately develop cirrhosis and end stage liver disease. In the middle of the spectrum are many patients who have few or no symptoms, mild to moderate elevations in liver enzymes, and an uncertain prognosis.

Risk Factors

The hepatitis C virus is spread primarily by contact with blood and blood products. At present, injection drug use is the most common risk factor for contracting the disease. However, many patients acquire hepatitis C without any known exposure to blood or to drug use.

Sexual Transmission

Sexual transmission of hepatitis C between monogamous partners appears to be uncommon. Spread of hepatitis C to a spouse or partner in a stable, monogamous relationship occurs in less than 1 percent of partners per year. For these reasons, changes in sexual practices are not recommended for monogamous patients. People with multiple sex partners should be advised to follow safe sex practices, which should protect against hepatitis C as well as hepatitis B and HIV.

Sporadic Transmission

Sporadic transmission, when the source of infection is unknown, occurs in about 10 percent of acute hepatitis C cases and 30 percent of chronic hepatitis C cases. These cases are usually referred to as sporadic or community-acquired infections. These infections may have come from exposure to the virus from cuts, wounds or medical procedures.

Clinical Symptoms

Many people with chronic hepatitis C have no symptoms of liver disease. If symptoms are present, they are usually mild, nonspecific, and intermittent. They may include:

- ❖ Fatigue
- ❖ Mild right-upper-quadrant discomfort or tenderness
- ❖ Nausea
- ❖ Poor appetite

- ❖ Muscle and joint pains

Similarly, the physical exam is likely to be normal or show only mild enlargement of the liver or tenderness.

Clinical Features of Cirrhosis

Once a patient develops cirrhosis or if the patient has severe disease, symptoms and signs are more prominent. In addition to fatigue, the patient may complain of muscle weakness, poor appetite, nausea, weight loss, itching, dark urine, fluid retention, and abdominal swelling. Physical findings of cirrhosis may include:

- ❖ Enlarged liver
- ❖ Enlarged spleen
- ❖ Jaundice
- ❖ Muscle wasting
- ❖ Skin abrasions
- ❖ Ascites or abdominal fluid buildup
- ❖ Ankle swelling

Other complications of chronic hepatitis C are:

- ❖ Glomerulonephritis – inflammation of the kidney
- ❖ Porphyria cutanea tarda – hyperpigmentation generally of the face

Testing for Hepatitis C Virus

Several methods are available for measuring the concentration or level of virus in serum, which is an indirect assessment of viral load. When performed carefully, quantitative assays provide important insights into the nature of hepatitis C. Most patients with chronic hepatitis C have levels of hepatitis C virus RNA (ribonucleic acid) - also known as viral load - between 50,000 to 5 million IU (international units) per ml.

Viral levels as measured by **hepatitis C virus RNA (HCV RNA)** do not correlate with the severity of the hepatitis or with poor prognosis; but viral load does correlate with the likelihood of a response to antiviral therapy. Rates of response to a course of peginterferon and ribavirin are higher in patients with low levels of HCV RNA. The usual definition of “low levels” is below 1 million IU per ml. In addition, monitoring HCV RNA levels during the early phases of treatment may provide early information on the likelihood of response.

Hepatitis C Genotypes

There are 6 known genotypes of hepatitis C, knowing the genotype of hepatitis C is helpful in making recommendations regarding therapy. Patients with genotypes 2 and 3 are two to three times more likely to respond to interferon/ribavirin-based therapy than patients with genotype 1 – most patients with genotype 2 or 3 are curable. Once the genotype is identified, it need not be tested again; genotypes do not change during the course of infection.

Liver Function Tests

There are simple blood tests that can be performed that can also contain indicators of hepatitis C virus infection, all related to the liver function. In chronic hepatitis C, increases in the **alanine aminotransferase (ALT)** and **aspartate aminotransferase (AST)** range from 0 to 20 times the upper limit – generally will be less than 5 times the upper limit. **ALT** levels are usually higher than **AST** levels, but that finding may be reversed in patients who have cirrhosis.

Liver Biopsy

Liver biopsy is not necessary for diagnosis but is helpful for grading the severity of disease and staging the degree of fibrosis and permanent damage of the liver. Hepatitis C virus causes necrosis and inflammation in parts of the liver and can lead to fibrosis or the formation of fibrous tissue in parts of the liver which can lead to further liver damage.

ALT levels, particularly if tested over an extended period, are reasonably accurate reflections of disease activity and the impact that the disease has on the liver. Patients with repeatedly normal ALT levels usually show mild necrosis and inflammation on a liver biopsy. Patients who maintain ALT levels above 5 times the upper limit of normal usually have marked necrosis and inflammation on a liver biopsy. For this reason the physician may not want to perform a liver biopsy in some cases and rely on the less invasive liver function lab tests to monitor liver disease.

Diagnosis of the Disease

Hepatitis C is most readily diagnosed when serum aminotransferases (ALT and AST) are elevated and anti-HCV is present in serum. The diagnosis is confirmed by the finding of HCV RNA in serum.

Acute hepatitis C is diagnosed on the basis of symptoms such as jaundice, fatigue, and nausea, along with marked increases in serum ALT and presence of anti-HCV.

Chronic hepatitis C is diagnosed when anti-HCV is present and serum aminotransferase levels remain elevated for more than 6 months. Testing for HCV RNA confirms the diagnosis and documents that the virus is present; almost all patients with chronic infection will have the viral genome detectable in serum when tested.

Treatment of Hepatitis C

Pegylated alpha interferon (peginterferon), generally in combination with the anti-viral medication ribavirin is the treatment of choice at this time. Alpha interferon is a host protein that is made in response to viral infections and has a natural antiviral activity. Peginterferon is alpha interferon that has been modified chemically by the addition of a large inert molecule of polyethylene glycol. Pegylation changes the uptake, distribution, and excretion of interferon, prolonging its time that it remains in the body and is effective. Peginterferon can be given once weekly and provides a constant level of interferon in the blood. Peginterferon is more active than standard interferon in inhibiting HCV and yields higher sustained response rates with similar side effects.

Ribavirin is an oral antiviral agent, given twice daily with meals, that has activity against a broad range of viruses. By itself, ribavirin has little effect on HCV, but adding it to therapy with peginterferon increases the sustained response rate by two to three fold. For these reasons, combination therapy is now recommended for hepatitis C, and interferon alone is applied only when there are specific reasons not to use ribavirin.

Combination therapy leads to rapid improvements in serum ALT levels and disappearance of detectable HCV RNA in up to 70 percent of patients. Long-term improvement in hepatitis C occurs only if HCV RNA disappears during therapy and stays undetectable once therapy is stopped. Among patients who become HCV RNA negative during treatment, a proportion relapses when therapy is stopped. The relapse rate is lower in patients treated with combination therapy compared with peginterferon alone. Studies have shown that a 48-week course of combination therapy using peginterferon and ribavirin yields a sustained response rate of approximately 55 percent. A similar course of peginterferon alone yields a sustained response rate of only 35 percent. A response is considered “sustained” if HCV RNA remains undetectable for 6 months or more after stopping the therapy. This is another reason that combination therapy is generally used (both peginterferon and ribavirin) versus peginterferon alone and the patient should remain extremely compliant with both medications.

For patients treated with combination therapy, the optimal duration of treatment depends on the viral genotype. Patient with genotypes 2 and 3 have a high rate of response to combination treatment (70 to 80 percent), as a 24-week course of combination therapy yields results equivalent to those of a 48-week course. In contrast, patients with genotype 1 have a lower rate of response to combination therapy (40 to 45 percent), and a 48-week course yields a significantly better sustained response rate.

In addition, the optimal dose of ribavirin appears to vary depending on genotype. For patients with genotype 2 or 3, a dose of 800 mg daily appears adequate. For patients with genotype 1, the full dose of ribavirin (1,000 to 1,200 mg daily depending on body weight) appears to be needed for an optimal response.

Who Should be Treated

The National Institute of Health Consensus Development Conference Panel recommended that therapy for hepatitis C be limited to those patients who have histological evidence of progressive disease. Thus, the panel recommended that all patients with fibrosis or moderate to severe degrees of inflammation and necrosis on liver biopsy should be treated and that patients with less severe histological disease be managed on an individual basis. Patient selection should not be based on the presence or absence of symptoms, the mode of acquisition, the genotype of HCV RNA, or the serum HCV RNA levels. It is up to your physician to make the determination if you are appropriate for treatment, based on the clinical findings and your physical condition at the time of diagnosis.

Because such a high proportion of patients with acute infection develop chronic hepatitis C, prevention of chronicity has become a focus of attention. **In some clinical studies, 83 to 100 percent of persons treated within 1 to 4 months of onset of acute hepatitis C, have had resolution of the infection. For this reason it is important that therapy be initiated as soon as possible and that the patient remains compliant with the therapy prescribed.**

Strict abstinence from alcohol is recommended during therapy with interferon. Interferon therapy can be associated with relapse in people with a previous history of drug or alcohol abuse. If there is a history of alcohol abuse, typically there needs to be a 6-month abstinence period before starting the interferon therapy.

Patients receiving therapy with peginterferon with or without ribavirin should use strict birth control during the course of therapy and for at least 6 months after completing the therapy to prevent any pregnancies that could result in birth defects and/or transmission of hepatitis C to the fetus. It is generally best to employ two methods of birth control, such as a birth control pill as well as a condom or a spermicidal cream along with a condom, etc.

Alpha interferon therapy can induce autoantibodies, and a 24 to 48 week course triggers an autoimmune condition in about 2 percent of patients. This can result in the exacerbation or

worsening of a known autoimmune disease (such as rheumatoid arthritis or psoriasis) occurs commonly during interferon therapy.

Common Side Effects of Treatment

Common side effects of peginterferon therapy – occurring in more than 10 percent of the patients – include:

- ❖ Fatigue
- ❖ Muscle aches
- ❖ Headaches
- ❖ Nausea and vomiting
- ❖ Skin irritation at the injection site
- ❖ Low-grade fever
- ❖ Weight loss
- ❖ Irritability
- ❖ Depression
- ❖ Mild bone marrow suppression
- ❖ Hair loss

Most of these side effects are mild to moderate in severity and can be managed. They are worse during the first few weeks of treatment, especially with the first injection. Thereafter, side effects diminish. Acetaminophen may be helpful for the muscle aches and low-grade fever. Fatigue and depression are occasionally so troublesome that the dose of interferon should be decreased or on rare occasions therapy may have to be stopped early. Generally the psychiatric side effects such as irritability and depression resolve within 2 to 4 weeks of completing combination therapy. Patients that do show signs of depression may benefit from antidepressant therapy using selective serotonin reuptake inhibitors while on peginterferon treatments.

Ribavirin also causes side effects, and is generally used in combination with peginterferon. The most common side effects of ribavirin are:

- ❖ Anemia
- ❖ Fatigue and irritability
- ❖ Itching
- ❖ Skin rash
- ❖ Nasal stuffiness, sinusitis, and cough

Your doctor may choose to prescribe medications that help to reverse or resolve the anemia, if the anemia becomes severe. Studies have shown that this is often a better alternative for hepatitis C therapy than is decreasing the dose of the ribavirin or stopping the ribavirin all together.

Note: 6 months after stopping therapy, you should be tested for HCV RNA. If this test is still negative after this 6 month period, the chance of a long term “cure” or eradication of the disease is excellent; relapses have rarely been reported after this point.

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