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# Chronic hepatitis C: a clinical overview

## KEY POINTS:

Because hepatitis C virus (HCV) infection is so common, it may be the most important cause of hepatocellular carcinoma worldwide.

Present serologic tests for anti-HCV antibodies are sensitive but lack specificity; positive results should be interpreted in light of whether the patient has risk factors for HCV infection and aminotransferase elevations.

Interferon has low efficacy in treating chronic HCV infection, and studies have shown a disappointingly high relapse rate after treatment has ended. Researchers are trying to identify new antiviral agents for monotherapy or combination therapy, and viral or host factors that may predict response to treatment.

HCV cannot integrate itself into the host's genome, but has a remarkable capacity to mutate, producing multiple coexisting strains or quasispecies. The host cannot contain the resistant mutant strains, and thus fails to build a protective immune response. This has hindered efforts to develop an effective vaccine against HCV.

**ABSTRACT:** Recent advances in analyzing hepatitis C virus (HCV) have improved understanding of how it causes chronic liver disease, although the exact rate of disease progression and factors influencing its natural history are not entirely known. Tests for HCV fall into two categories: serologic and virologic. Interferon has shown limited efficacy in treating chronic HCV infection, and various strategies are being tried to improve its efficacy. HCV-related cirrhosis and liver failure have become one of the most common indications for liver transplantation in the United States.

In the relatively brief interval since HCV was isolated and cloned in 1989, extraordinary advances in serologic and molecular techniques have elucidated HCV's role in chronic liver disease and improved our ability to detect the virus and identify its subtypes.

Most HCV infections become chronic, although the natural history and rate of progression of chronic HCV infection are not entirely clear. The newest clinical research is disclosing what viral and host characteristics may affect the severity of the disease, efficacy of therapy, and whether a patient will go on to develop cirrhosis, hepatocellular carcinoma, or other complications of end-stage liver disease.

## HCV MUTATES RAPIDLY TO EVADE IMMUNITY

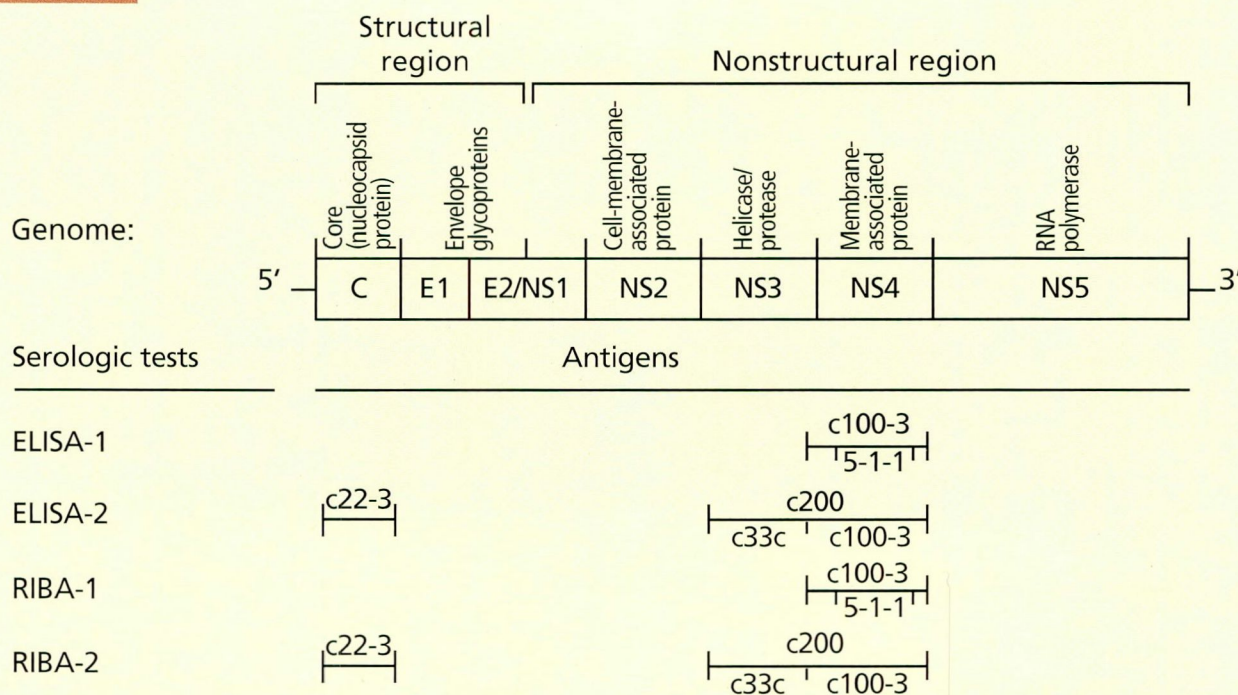
### Description of HCV

HCV is a positive-strand RNA virus related to the *Flaviviridae*. Its genome contains approximately 9500 bases, which code for approximately 3000 amino acids.<sup>1-4</sup> It has no DNA intermediate. Its RNA contains a 5' untranslated region, structural components coding for the nucleocapsid and envelope, and nonstructural components coding for proteins with different enzymatic functions (FIGURE 1). This single, open reading frame encodes for a large polypeptide precursor that is cleaved into different proteins.<sup>1</sup>

There are probably 10 major groups (types) and 30 subgroups (subtypes) of HCV. The prevalence of different genotypes varies in different geographic areas; types 1a and 1b predominate in the United



FIGURE 1



Structure of the hepatitis C virus genome, showing the genes coding for the antigens used by current serologic tests. ELISA, enzyme-linked immunosorbent assay; RIBA, recombinant immunoblot assay.

States, 1b predominates in Asia, 3b occurs only in Japan, and genotype 4 predominates in the Middle East.

The relationship between genotype, severity of disease, and response to treatment is being slowly clarified. For example, genotype 1b is thought to be associated with higher levels of viremia, poor response to interferon treatment, and may cause more aggressive disease.

#### How HCV evades immunity

Unlike hepatitis B, HCV cannot integrate itself into the host's genome. Instead, it uses another strategy to persist inside the host—a remarkable capacity to mutate under the pressure of host immunity or therapy, producing multiple coexisting strains or quasispecies.<sup>3</sup> The host produces antibodies against specific strains, but cannot contain the development of resistant mutant strains, and thus fails to build a protective immune response. A previously infected host can be reinfected with the

same or different strains of the virus; this inability to develop protective immunity has hindered efforts to develop an effective vaccine against HCV.<sup>1-4</sup>

#### ■ HOW CHRONIC HCV INFECTION DAMAGES THE LIVER

HCV infection may damage the liver by two mechanisms: a direct cytopathic effect and an immunologically mediated one. The cytopathic effect may explain how the liver disease progresses in immunocompromised patients; support for this hypothesis comes from the pattern of histologic injury found in this disease—predominantly lobular hepatitis with scarce periportal and piecemeal necrosis.

Cytotoxic T cells are implicated in immunologically mediated liver damage. In chronic HCV infections, CD4<sup>+</sup> T lymphocytes respond to all the viral proteins; the core and NS4 proteins may be most immunogenic, but the response appears to be polyclonal and

nonspecific.<sup>5,6</sup> This CD4+ (and CD8+) T-lymphocyte response may result in cell-mediated injury to the liver parenchyma, and HCV's direct cytopathic effect may intensify the injury. Differences among individuals in their immune reactions and susceptibility to the cytopathic effect of HCV, and differences among specific strains of HCV, may explain why HCV infection varies in its course.

## SEVERE IMPACT OF HCV: EPIDEMIOLOGY AND NATURAL HISTORY

The impact of HCV infection is enormous, imposing a tremendous economic and social burden in direct costs of care; indirect costs of early mortality, morbidity, and years of work lost; and intangible costs of pain and suffering.<sup>7</sup>

HCV accounts for 16% to 21% of all cases of acute hepatitis in the United States, and 45% of all cases of chronic viral hepatitis. Some 4.0 million Americans carry the virus, and approximately 30,000 acquire it each year.<sup>8,9</sup> The overall prevalence of HCV infection is 1.8%, varying from as low as 0.5% in low-risk blood donors to as high as 60% to 90% in intravenous drug abusers.

### Risk factors

A 1990–1993 study from the Centers for Disease Control and Prevention (CDC) found that 38% of patients with acute HCV infection were intravenous drug abusers, 4% had received blood transfusions, 1% were on dialysis, 2% had occupational exposure to HCV, and 10% had sexual or household exposure. However, as many as 40% of HCV-infected persons have no identifiable risk factor. Low socioeconomic status, body piercing, tattooing, and intranasal cocaine use have all been implicated as potential risk factors.<sup>8</sup>

**Accidental needle sticks** in health care workers impart a risk of HCV transmission of 0% to 6% as measured by antibody seroconversion and up to 10% as measured by HCV RNA tests.<sup>8,10</sup>

**Sexual exposure** carries an uncertain risk. Serologic tests were positive in 0% to 15% of partners of 419 infected patients in 12 studies.<sup>8</sup> Sexual transmission of HCV is probably very inefficient, but may be more likely if the partner has a high viral burden or if the proband has multiple sexual partners. Currently, the CDC has no specific recommendations regarding sexual transmission of HCV, but persons with multiple sexual partners should be advised to practice safe sex. An

untested partner in a monogamous relationship with a person with HCV infection should probably undergo testing for it, be advised about the uncertainties of the risk of sexual transmission, and be given information about protective measures, such as condoms.<sup>1</sup>

**Vertical transmission.** The risk of vertical transmission of HCV is fraught with even more uncertainty. HCV seroprevalence ranges from 0% to 13% in the newborns of HIV-negative, HCV-positive mothers.<sup>8</sup> A greater percentage of newborns may actually be infected (and would be identified if they underwent HCV RNA testing), but do not acquire chronic infections. Perinatal transmission may be more likely if the mother has a high HCV RNA titer or is HIV-positive.<sup>1,8</sup>

### Progression of disease

Acute HCV infection can progress to chronic hepatitis and cirrhosis, but the rate of progression and the time from exposure to cirrhosis and its complications (liver failure and hepatocellular carcinoma) are still not known. Studies are in progress to elucidate the characteristics of the virus (ie, genotype, viral load), the host (ie, alcohol consumption, high hepatic iron load), and the natural progression of the disease that affect prognosis.

**Hepatocellular carcinoma**, the most dreaded complication of HCV infection, has a strong and established association with HCV infection.<sup>11,12</sup> An NIH consensus conference in March 1997 estimated the risk of developing hepatocellular carcinoma at 1% to 5% over 20 years for a person with chronic HCV infection. Once cirrhosis is established, the rate of hepatocellular carcinoma increases to 1% to 4% per year.

Because HCV infection is so common, it may be the most important cause of hepatocellular carcinoma worldwide. Biopsy studies suggest that 20% of individuals with chronic HCV infection develop liver failure or hepatocellular carcinoma. According to these estimates, 7000 to 9000 persons in the United States may suffer HCV-related liver failure and hepatocellular carcinoma each year.<sup>8,9,13,14</sup>

How HCV causes cancer is not known. Since HCV is an RNA virus and cannot integrate into the host's genome, the inflammation caused by the chronic viral infection may be the culprit. Unlike hepatitis B infection, virtually all HCV-related hepatocellular carcinoma occurs with cirrhosis.<sup>1,11,12</sup>

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**TABLE 1**

### DISEASES ASSOCIATED WITH CHRONIC HEPATITIS C INFECTION

Rheumatoid arthritis  
Salivary gland lesions  
Porphyria cutanea tarda  
Mooren's corneal ulcers  
Essential mixed cryoglobulinemia  
Vasculitis  
Glomerulonephritis  
Autoimmune hepatitis

**TABLE 2**

### CONDITIONS CAUSING FALSE-POSITIVE RESULTS ON ENZYME-LINKED IMMUNOSORBENT ASSAY (ELISA) FOR ANTI-HEPATITIS C VIRUS ANTIBODIES

Immune-mediated disorders  
Systemic lupus erythematosus  
Primary biliary cirrhosis

Conditions causing hyperglobulinemia  
Rheumatoid arthritis  
Autoimmune hepatitis  
Myeloma  
Parasitic infections

Human immunodeficiency virus infection

Immunosuppression after organ transplantation

Other liver diseases  
Alcoholic liver disease  
Acute viral hepatitis (non-C hepatitis)  
Porphyria cutanea tarda

Improper serum storage

### Other HCV-associated diseases

Several other conditions have been associated with HCV (TABLE 1), although the role of HCV (or of the underlying immunologic disruption caused by the chronic infection) is not understood.

In a series of patients with essential mixed cryoglobulinemia, 84% were HCV RNA-positive.<sup>1,15</sup> Acquired porphyria cutanea tarda is also strongly associated with HCV infection: 62% to 82% of such patients are seropositive for HCV, and 66% are positive by HCV RNA testing. Membranoproliferative glomerulonephritis, lichen planus, and Mooren's corneal ulcers are other associated disorders.<sup>15</sup>

### ■ DIAGNOSING HCV INFECTION

Most patients with chronic HCV infection have no symptoms and only minimal aminotransferase elevations (usually < 1000 U/L),<sup>1,4,8,9,13-18</sup> and an estimated 33% of infected persons have normal aminotransferase levels. However, some biopsy studies have found

that 20% to 30% of infected patients have cirrhosis.<sup>19-21</sup> Because HCV infection is so common, any patient with persistently elevated aminotransferase levels should be tested for it.

Tests for HCV fall into two categories: serologic and virologic.<sup>2,22</sup>

### Serologic tests for anti-HCV antibodies

Serologic tests detect antibodies against various viral antigens, but cannot distinguish between active infection and immunity. Their accuracy depends on the prevalence of infection in the population tested. The enzyme-linked immunosorbent assay (ELISA) is the first-line serologic test; the recombinant immunoblot assay (RIBA) is the most commonly used supplemental assay.

ELISAs are fairly simple, reproducible, and inexpensive. The first-generation ELISA (ELISA-1) used two HCV recombinant antigens (FIGURE 1). Although its sensitivity in volunteer blood donors (a low-risk group) was 95% to 98%, its specificity was low, leading to a high false-positive rate. Used in screening blood donors, this test detects 5 to 8 cases per 1000 donor units.

The second-generation ELISA (ELISA-2) uses more antigens and has a sensitivity of 92% to 95%, using HCV RNA testing by PCR as the reference standard (see below). In volunteer blood donors, ELISA-2 detects another 2 to 2.4 cases per 1000 donor units. However, in low-risk persons, 39% to 50% of positive ELISA results may be false-positive, requiring confirmation with highly specific supplemental assays. TABLE 2 lists conditions that can produce false-positive ELISA results.<sup>2,22</sup>

**RIBAs as supplemental assays.** The second-generation RIBA (RIBA-2) uses the same antigens as does ELISA-2 (FIGURE 1). In this nitrocellulose-based system, the reactivity of antibodies toward each antigen band is reported as 1+ to 4+. If two or more bands react with an intensity of at least 1+, the test is considered positive. If only one band is positive, the result is considered intermediate. An intermediate reaction to the c22-3 or c33c bands is strongly associated with HCV RNA and may represent actual viremia.<sup>22</sup>

Investigators are attempting to determine if certain antibody subclasses, such as IgM, might predict response to treatment or distinguish between acute and chronic HCV infection. However, such testing remains investigational.<sup>22,23</sup>

# Beyond hepatitis C: new blood-borne viruses

Technologic advances in the past 3 decades have led to the discovery and characterization of a multitude of new hepatotropic viruses responsible for most cases of acute and chronic hepatitis. For example, discovery of the hepatitis C virus (HCV) and implementation of HCV testing of blood products have led to a substantial reduction in transfusion-related HCV infections, from 0.19% to 0.03% per unit transfused.<sup>1</sup>

Nevertheless, despite these breakthroughs, many patients have hepatitis with none of the known viral agents (A, B, C, D, or E). A recent review estimated that non-ABC hepatitis accounted for 2% of cases of acute hepatitis, 17% of chronic hepatitis, 68% of transfusion-related hepatitis, and 31% of fulminant hepatitis.<sup>2</sup> Therefore, the search for agents other than the known viruses continues.

Many systemic viruses (Epstein-Barr, cytomegalovirus, varicella, rubella) can cause acute but not chronic hepatitis. In 1996, two new hepatotropic viruses—hepatitis G and GB—were discovered and implicated in causing both acute and chronic liver disease. Defining the epidemiologic and clinical importance of these viruses and discovering additional viral agents in the future will help us in managing patients with liver disease.

The following discussion reviews these new viruses and their possible association with acute and chronic liver disease.

## ■ INITIAL DISCOVERY

Over the past 3 decades, the serum of a young surgeon (G.B.) who developed icteric hepatitis in the 1960s was used to infect laboratory animals, leading to the discovery, cloning, and characterization of three distinct "GB" viruses: GBV-A, GBV-B, and GBV-C. Although all three can infect animals, only GBV-C is definitely associated with chronic infection and hepatitis in humans.<sup>3</sup>

Also characterized and cloned in 1996 was another transfusion-transmissible agent, hepatitis G virus (HGV).<sup>4</sup> Both the GB viruses and HGV are now considered to belong to the *Flaviviridae* family of hepatotropic viruses. Polypeptide and nucleotide comparisons show that there is only 26% to 48% viral polypeptide homology between GBV-A, GBV-B, GBV-C, and HCV. However, polypeptide homology is 97% between HGV and GBV-C, and only 28% between HGV and HCV. HGV and GBV-C are now considered different genotypes of the same virus and distinct from HCV.<sup>2</sup>

The genomic organization of HGV is similar to that of HCV, containing 9392 nucleotides encoding for a polypeptide of 2873 amino acids. As in HCV, genes encoding for structural proteins are located in the 5' end of the genome, and nonstructural genes are located in the 3' end.<sup>3</sup>

## ■ EPIDEMIOLOGY

Of patients infected with HCV, 10% to 20% also have detectable HGV RNA.<sup>2</sup> Cross-sectional studies of high-risk populations (intravenous drug users, hemodialysis patients, and hemophiliacs) have shown a relatively high prevalence of HGV RNA (10% to 30%).<sup>2</sup> These studies indicate that HGV infection is common, and its risk factors are similar to those for other transfusion-related viruses.

Multiple studies have estimated the prevalence of HGV infection in different patient populations in the United States and Europe. Although serologic tests are being developed, most of the prevalence studies used RNA testing by polymerase chain reaction (PCR). HGV RNA was detected in about 13% of persons with acute non-A-E hepatitis and 8% to 12% with chronic non-A-E hepatitis.<sup>2</sup>

The prevalence of HGV infection in "cryptogenic cirrhosis" ranged between 8% and 12%; in hepatitis after transfusion, 1.7% to 5%.<sup>2,5</sup> However, this prevalence was 18% to 20% in patients with multiple transfusions.<sup>2,6</sup>

Of interest, healthy blood donors with normal alanine aminotransferase (ALT) levels had an estimated prevalence of HGV of 1.5% to 1.7%; those with ALT levels greater than 45 IU/mL had a prevalence of 2.3%.<sup>4,5</sup> These data indicate the prevalence of this virus in healthy blood donors is not higher in persons with elevated aminotransferase levels.

## ■ NATURAL HISTORY AND CLINICAL CONSEQUENCES

HGV appears to cause mild hepatitis, with chronic viremia documented to persist for up to 9 years. In liver transplant recipients, HGV prevalence is estimated at 53% to 63%, although infected transplant recipients do not appear to have a higher incidence of hepatitis or a lower survival rate.<sup>2,7</sup> Patients coinfecting with both HCV and HGV do not appear to have a faster rate of progression or lower rate of response to interferon treatment.<sup>8</sup> Up to 40% of infected persons have normal serum aminotransferase levels, and 65% have no evidence of liver disease.<sup>2,9-11</sup> In addition, lack of association between infectivity (as evidenced by HGV RNA positivity) and abnormal aminotransferase levels in healthy blood donors even further suggest that HGV infection may follow a benign course.<sup>2</sup>

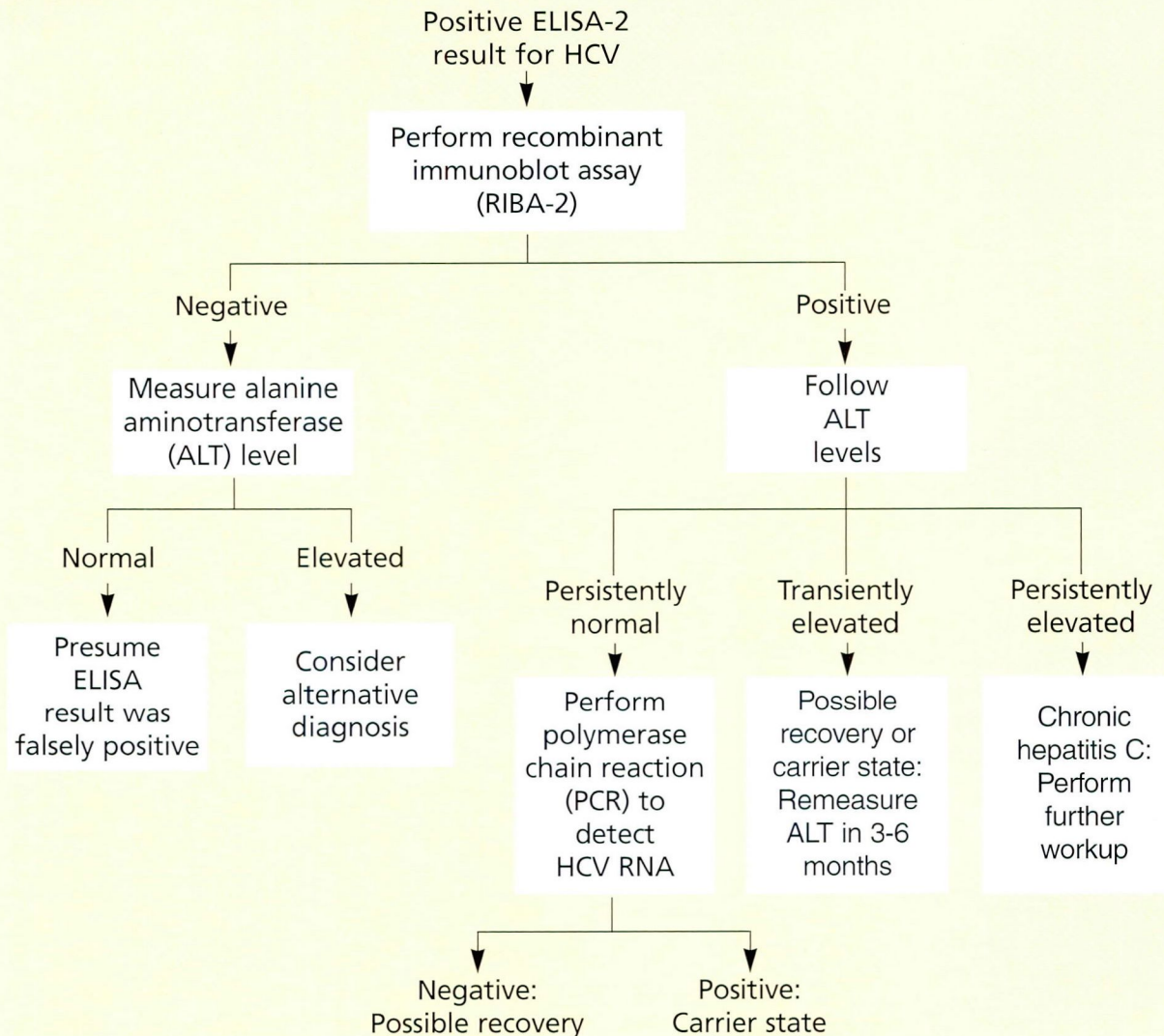
A consensus is growing that despite high rates of persistent viremia, chronic HGV-related liver disease may be uncommon. Whether HGV or GBV-C infection can lead to significant liver disease or cirrhosis is not entirely clear, and further longitudinal studies are needed to document their clinical course.

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FIGURE 2



Suggested algorithm for diagnosing hepatitis C virus (HCV) infection.

**Problems with serologic testing.** Despite improvements in serologic testing, several problems remain.

- The FDA-approved second-generation ELISA can still give false-negative results in acute HCV infection. A third-generation ELISA test, currently in use in Europe, incorporates an antigen from the NS-5 region of the HCV genome and may detect antibodies against HCV earlier during an acute HCV episode (an average improvement of 3 to 4

weeks). Although ELISA-3 was recently approved by the FDA, RIBA-3 is not yet available. ELISA-3 may soon become a useful diagnostic test for individuals in whom seroconversion takes longer.

- The predictive value of the ELISA-2 supplemented by the RIBA-2 is high in high-risk patients with elevated transaminase levels and virtually establishes the diagnosis of HCV infection. However, these tests have lower specificity in low-risk patients.

- As mentioned above, serologic tests only detect antibodies and cannot differentiate between active infection and immunity. This distinction is especially pertinent to patients with positive serologic test results but persistently normal transaminase levels.<sup>2,22</sup> In all of the above groups of patients, HCV RNA testing, the most sensitive method of detecting the actual virus (and therefore the “gold standard”), may help establish actual HCV viremia.

### Tests for HCV RNA

Measuring HCV RNA can help establish the diagnosis of acute hepatitis C in patients without detectable antibodies. Another use is in patients with positive serologic test results but persistently normal transaminase levels (who may have recovered from HCV infection and cleared the virus, or who may be “healthy carriers” of the virus). Some HCV RNA tests give quantitative results, others are qualitative. HCV RNA quantification may be important in predicting response to interferon therapy,<sup>22–24</sup> the rate of disease progression, and the incidence of recurrence of HCV after liver transplantation.

The polymerase chain reaction (PCR), which uses target amplification to measure HCV RNA, is the most sensitive method of detecting viral levels of less than 1000 genome equivalents/mL. Both qualitative and quantitative PCR tests are available.

The branched DNA (b-DNA) signal-amplification method (Quantiplex 2.0, Chiron), in contrast, can only detect levels of viremia greater than 200,000 genome equivalents/mL.<sup>1,4,22,25,26</sup>

### A strategy for diagnosing HCV infection

When a patient has a positive ELISA-2 result, our laboratory performs a RIBA-2 (FIGURE 2). In a low-risk patient, if the RIBA result is negative and if aminotransferase levels are not elevated, the ELISA result was probably false-positive. If the supplemental RIBA test is negative but the aminotransferase levels are elevated, one should look for another cause of liver disease. If the supplemental RIBA is positive and the patient has persistently elevated aminotransferase levels, chronic HCV infection is the most likely diagnosis, and further workup and therapy should be undertaken. If aminotransferase levels are transiently elevated, they should be monitored periodically. If aminotransferase levels are persistently elevated, chronic HCV infection is presumed.

For patients with positive ELISA and RIBA test results but persistently normal aminotransferase levels, HCV RNA testing by PCR can distinguish HCV carriers from those who have recovered from the infection. PCR testing can still miss a few patients with extremely low levels of HCV RNA, but in the presence of normal aminotransferase levels, the importance of this state is unknown. For all practical purposes, unless such patients will be treated with immunosuppressive agents, recovery may be presumed and no further management can be recommended.

### Liver biopsy

Liver biopsy is the only way to directly assess the degree of inflammation and damage that may have occurred consequent to HCV infection. The pathologic findings in acute HCV infection are indistinguishable from those in other types of acute viral hepatitis, but may feature more bile duct injury, steatosis, and lymphoid aggregates.<sup>27</sup> Histologic findings associated with chronic HCV infection are nonspecific but can range from mild inflammation to well-established cirrhosis. Liver biopsy findings do not always correlate with symptoms or levels of aminotransferase elevations. Patients with mild inflammation or well-established cirrhosis can present without any specific symptoms or with minimally elevated and fluctuating aminotransferase levels.

Although liver biopsy is important in assessing the severity of liver injury (a possible prognostic factor), highly sensitive serologic and RNA tests make it less important for diagnosing HCV infection.<sup>22,24,25,28</sup> Most experts recommend a pretreatment liver biopsy, although it is not mandatory.<sup>1,22</sup>

When a patient has a positive ELISA-2 result, obtain a RIBA-2

## ■ TREATING HCV WITH INTERFERON

Multiple trials have established the efficacy of interferon for treating chronic HCV infection.<sup>1,13,29–35</sup> In contrast, its efficacy for treating acute HCV hepatitis is not well established, although several studies in acute hepatitis after transfusion showed promising results. At present, interferon is approved only for treating chronic HCV infection<sup>32</sup>; candidates must have chronic HCV infection with elevated aminotransferase levels for at least 6 months and no contraindications to treatment (TABLE 3).

How interferon works is not understood. It may have both direct antiviral effects (by



TABLE 3

### RELATIVE CONTRAINDICATIONS TO INTERFERON THERAPY

Leukopenia (polymorphonuclear  
leukocytes  $< 0.75 \times 10^9/L$ )

Thrombocytopenia ( $< 75 \times 10^9/L$ )

Severe psychiatric disorders

Decompensated liver disease

Terminal comorbid conditions

Unreliable patients

History of autoimmune disease

inducing enzymes that interfere with the production of viral proteins and their subsequent replication) and immunomodulatory effects (by enhancing HLA-I restricted cellular immunity and viral clearance).<sup>33</sup>

In initial trials in chronic HCV infection, interferon alfa 2b in a dosage of 3 million units three times per week for 6 months resulted in complete response rates of 40% to 70%. These trials used biochemical response (ie, a decrease in aminotransferase levels) as the efficacy endpoint and classified patients as "complete responders," "partial responders," and "nonresponders." Subsequent follow-up studies showed a disappointingly high relapse rate of more than 50% after treatment was stopped.

Currently, responses to interferon are divided into several patterns: end-of-treatment response (with enzyme levels returning to normal at the end of treatment); sustained response (with enzyme levels returning to normal after treatment and remaining normal at least 6 months); relapse (with aminotransferase levels returning to normal after treatment but with subsequent biochemical or virologic evidence of recurrence); and nonresponse (with aminotransferase levels remaining elevated).

#### Interferon dosage

The most common interferon dosage in chronic HCV infection is 3 to 5 million units three times a week for 6 months. The dosage and the duration of therapy can be adjusted on the basis of response and side effects. Under these circumstances, interferon has a 15% to 20% sustained response rate. Increasing the duration of treatment to 12 months increases the sustained response rate to 20% to 30%. Short-term (12 to 14 months) follow-up studies found that most sustained responders remain in remission. There is also some evidence that those who achieve sustained response also lose HCV RNA and have histologic improvement. Due to relatively short fol-

low-up, there are no available data on the impact of therapy on the overall mortality rate.<sup>1,30-32</sup>

#### Side effects of interferon

The most common side effect of interferon is a flu-like syndrome, which occurs in more than 10% of patients. These symptoms are treatable with nonsteroidal anti-inflammatory agents or acetaminophen. The severity of the symptoms decreases after the first 4 weeks of therapy. Other possible side effects of interferon therapy are noted in TABLE 4. Severe side effects requiring discontinuation or dose reduction are uncommon.<sup>32</sup>

#### Increasing the efficacy of interferon therapy

**Patient selection.** Because of interferon's relatively low efficacy in chronic HCV infection, investigators are searching for viral or host factors that may predict a better response to treatment. Three factors are consistently associated with response to treatment: absence of cirrhosis, favorable HCV RNA levels ( $< 2$  million copies/mL), and genotypes 2 or 3.<sup>19-24,28,32-39</sup> The utility of these factors in clinical practice is not established.

**Pretreatment.** Other strategies to enhance the efficacy of interferon are pretreatment with corticosteroids,<sup>40,41</sup> and phlebotomy to reduce iron levels.<sup>42-45</sup> Unfortunately, both have yielded either negative or conflicting results. It is also becoming clear that the type of interferon used (ie, natural or synthetic) does not affect the response to therapy.

**Increasing the dose.** Increasing the dose of interferon in an attempt to increase its efficacy results in more side effects and only a small gain in efficacy. In terms of duration of therapy, a 12-month course is now considered optimal to achieve sustained remission.

**Ribavirin.** A promising new strategy is to add ribavirin to interferon therapy. Ribavirin, a new nucleoside analogue, has no effect on viremia when used alone, but when used in combination with interferon can result in a sustained response rate of over 40%.<sup>46,47</sup> This combination is currently being tested in a series of multicenter, randomized, double-blind, placebo-controlled trials.

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**Future directions.** Better antiviral agents must be developed, as well as better strategies for using them in chronic HCV infection.

One of the potential targets of such new agents is the NS3 region of the HCV genome, a region that has protease activity that may be essential for viral replication. Specific protease inhibitors against HCV are under development and may become available for treatment of HCV as monotherapy or in combination with other agents.

Efficacy trials should concentrate not only on traditional biochemical endpoints but also on viral eradication, histologic improvement, prevention of cirrhosis, prevention of hepatocellular carcinoma, and ultimately, a cure for this infection. Great challenges remain to achieve these ambitious goals.

## HCV INFECTION AND LIVER TRANSPLANTATION

The past decade witnessed numerous advances in liver transplantation; better surgical techniques, postoperative care, and immunosuppression have led to 1-year survival rates of 85% and 3-year survival rates of 75% to 80%. HCV-related liver failure has become one of the most common indications for orthotopic liver transplantation in the United States.

### HCV infection almost always recurs after transplantation

PCR testing indicates that HCV infection recurs in almost all viremic patients after liver transplantation. Although long-term follow-up data are not available, one cohort study compared patients who received liver transplants because of HCV infection and patients who received transplants because of liver disease of uncertain origin, and found no significant differences in their 1-year or 3-year survival rates (87% vs 73% respectively).

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**TABLE 4**

### SIDE EFFECTS OF INTERFERON

<b>Systemic</b> Fatigue Myalgia Headache Anorexia, weight loss Nausea, vomiting Diarrhea Abdominal cramps Hair loss	<b>Psychologic</b> Anxiety Irritability Depression Social withdrawal Decreased libido Paranoid or suicidal ideation Return of craving for alcohol or drugs	<b>Autoimmune</b> Development of autoantibodies, anti-interferon antibodies Hyperthyroidism or hypothyroidism Vasculitis Other autoimmune disorders
<b>Neurologic</b> Difficulty concentrating Lack of motivation Sleep disturbance Delirium, disorientation Coma Seizures, electroencephalographic changes	<b>Hematologic</b> Decrease in platelets, white cells, hematocrit	<b>Other (rare)</b> Proteinuria Interstitial nephritis Nephrotic syndrome Cardiac arrhythmias Congestive heart failure Acute exacerbation of liver disease Retinal hemorrhage Hearing loss
<b>Infectious</b> Increased susceptibility to bacterial infection		

On biopsy, 44% to 67% of HCV-related transplant recipients have histologic evidence of inflammation. Most (80%) have mild pathologic findings, but 20% have severe inflammation, fibrosis, or cirrhosis. Only 2% of patients with HCV may require repeat transplantation.<sup>48</sup>

Although these studies suggest that HCV infection after transplantation follows a mostly benign course, the long-term results are not known. More recent data suggest that certain characteristics of the virus (genotype, viral load) may lead to a more aggressive recurrence of HCV and cirrhosis.

**Interferon treatment of recurrent HCV infection after transplantation** in patients with positive HCV RNA tests and with biopsy-proven inflammation, resulted in even lower efficacy rates than in immunocompetent patients. Interferon treatment can also increase the risk of rejection by increasing the expression of HLA-I and -II antigens. Trials of interferon in combination with ribavirin are currently underway. In short, most cases of recurrent HCV infection after transplantation are benign, but therapy may be needed for a subgroup of patients with more aggressive, progressive disease. ■



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