Clinician’s Guide to Hepatitis C

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Hepatitis C virus infection is common, often silent, and almost always chronic and can lead to cirrhosis and hepatocellular cancer. Deaths related to chronic hepatitis C are expected to increase dramatically in the future. Many cases of infection are asymptomatic and are undiagnosed because of a lack of recognition by patients and physicians. All patients currently or previously at risk of infection should undergo screening, including those who received blood transfusions before 1992. Interferon is the only effective therapy, but disappearance of virus is sustained in only 10 to 15% of patients. The combination of interferon and oral ribavirin therapy may increase the sustained response rate to about 40%. New agents such as hepatitis C virus-specific protease inhibitors may be available in the next 5 to 10 years, and treatment is evolving toward multiple-drug regimens analogous to those used for human immunodeficiency virus (HIV) infection. In contrast to public funding for drug development in HIV, such funding for hepatitis C has been limited.

Non-A, non-B hepatitis is now known as hepatitis C. Hepatitis B virus and hepatitis C virus (HCV) are parenterally transmitted, and both cause acute and chronic hepatitis. Although acute hepatitis B is self-limited in 90 to 95% of cases, acute hepatitis C is self-limited in only 10 to 15% of infections. Another important difference is that the level of virus in blood and body fluids is much higher with hepatitis B; thus, it is easier to transmit than is hepatitis C.

MAJOR PUBLIC HEALTH PROBLEM

Because 85% of people infected with HCV remain persistently infected, HCV is the most common cause of chronic viral hepatitis in the United States. The Centers for Disease Control and Prevention (CDCP) estimates that as many as 4 million Americans (1.5% of the population) are chronically infected with HCV. Because of the high rate of chronic infection and because many infected people are asymptomatic and unaware of their infection, chronic hepatitis C has become a major public health problem. One of every five people assessed in inner-city emergency departments is infected, as is one in three prison inmates. Chronic infection with HCV can lead to cirrhosis, liver failure, or hepatocellular carcinoma. In the United States, 10,000 deaths each year are related to chronic hepatitis C, and the CDCP expects this figure to triple during the next 10 to 20 years. Chronic hepatitis C is currently the leading indication for liver transplantation in the United States, accounting for 30% of cases. The 1995 estimates of the number of people infected in the United States, the cost to the economy, and the amount of research funding for the human immunodeficiency virus (HIV), hepatitis B virus, and HCV are shown in Table 1.

EPIDEMIOLOGY

The incidence of acute hepatitis C in the United States probably peaked at about 175,000 cases per year in 1989 and has now declined to about 30,000 cases per year. Nevertheless, a large number of people still have chronic HCV infection. Many HCV infections were acquired from transfusion of blood or blood products before the introduction of blood tests for HCV in 1990 through 1992. Today, the risk of HCV infection from a blood transfusion is only about 0.001% per unit transfused. Intravenous or intranasal drug use with sharing of paraphernalia now accounts directly or indirectly for about 60% of new infections. Other risk factors include sexual contact with an infected person, multiple sexual partners, low socioeconomic status, imprisonment, and occupational exposure; only about 5% of new infections are unexplained. Screening for HCV infection should be performed in groups with a high prevalence of HCV infection, including those with hemophilia, patients receiving hemodialysis, intravenous or intranasal drug users, patients in inner-city emergency departments, and long-term prisoners.

TRANSMISSION

Sexual Intercourse

The risk associated with a single sexual encounter is negligible, and the cumulative risk to an uninfected partner...
in a monogamous relationship for 10 to 20 years is only 5%. Because of the large number of sexual encounters in the population, however, the number of people infected through sexual contact is substantial. Thus, infected persons with multiple sexual partners should be advised to use barrier protection such as condoms. The rate of acquisition of HCV infection among nonsexual household contacts seems to be extremely small, and no cases of nonsexual direct transmission have been documented.

Maternal-Infant

The risk of maternal-infant transmission is 5% or less, except in cases of simultaneous HIV infection, and there are no recommendations against pregnancy for infected women. The infant may acquire anti-HCV antibody passively; thus, the antibody test is not good for screening during the first 6 months of life. The serum alanine aminotransferase (ALT) level is not reliably increased in infected infants; therefore, infants of infected mothers should undergo a qualitative test for HCV RNA (see subsequent discussion). There is no evidence that HCV is transmitted through breastfeeding.

Health-Care Workers

The risk of infection from a random needle stick in the hospital is about 0.1%; if the patient is known to be infected, the risk is 5 to 10%. Transmission from infected health-care workers to patients seems to be rare. Therefore, infection cannot be used as a barrier to employment, although a review of infection control procedures may be wise.

MOLECULAR BIOLOGY

HCV is a single-stranded RNA virus in the Flavivirus family. The RNA genome codes for a single polyprotein precursor containing at least three structural proteins and several nonstructural proteins, including a serine protease and an RNA polymerase (Fig. 1). The protease is necessary for splitting and releasing the active forms of the other functional proteins and therefore would seem to be a good target for future drug development. At least six main genotypes (species) and multiple subtypes of HCV exist. Genotype 1 accounts for about 70% of infections in the United States. Unfortunately, this genotype is associated with more progressive liver disease and is less likely to respond to treatment than other genotypes. The virus is prone to mutation, existing in a single individual as a heterogeneous population of slightly different genetic sequences termed "quasispecies." This genetic diversity enables the virus to escape the immune surveillance of the body and is probably the reason for the high rate of chronic infection.

CLINICAL SPECTRUM OF DISEASE

Liver Disease

During acute infection, only 25 to 35% of patients have symptoms (malaise, loss of appetite, and jaundice). HCV rarely causes fulminant liver failure. During the chronic phase, about 30% of patients become carriers but have no symptoms and have normal liver enzymes, 50% have no symptoms but increased liver enzymes, and 20% have clinical liver disease with symptoms of fatigue and malaise. Because chronic hepatitis C is typically a slow, smoldering process, no symptoms or physical signs may be noted for decades after infection. In some patients, the first signs and symptoms may be those associated with liver failure or portal hypertension, such as jaundice, ascites, and variceal bleeding, or hepatic encephalopathy.

Whether (with enough time) HCV infection causes progressive disease in all people or whether some remain healthy carriers indefinitely is unclear. Chronic hepatitis C leads to cirrhosis in about 20% of patients within 20 years of infection, although estimates of the risk of cirrhosis developing vary from 2 to 50%. The risk is increased by heavy alcohol consumption and is associated with age older than 40 years at the time of infection and male sex. After cirrhosis has been established, the 5-year survival rate is about 90% unless symptoms of liver failure or complications of portal hypertension occur, in which case the estimated 5-year survival rate decreases to 50%. Hepatocellular carcinoma is a recognized complication of chronic HCV infection, occurring at a median interval of 30 years after the initial infection. This disease almost always follows the development of cirrhosis, at which point the risk of cancer is 15 to 20% per decade. Cases of early and treatable hepatocellular cancer are being discovered by prospective surveillance. Many hepatologists screen their HCV-positive patients who have cirrhosis by obtaining the serum alpha-fetoprotein level and an ultrasound study of the liver every 6 to 12 months.

Table 1.—Estimated Prevalence, Economic Cost, and Research Funds in 1995 for Three Chronic Viral Illnesses in the United States

<table>
<thead>
<tr>
<th>Illness*</th>
<th>People infected (no.)</th>
<th>Annual cost ($)</th>
<th>Annual funds† ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV</td>
<td>900,000</td>
<td>Unknown</td>
<td>1,400,000,000</td>
</tr>
<tr>
<td>HBV</td>
<td>1,200,000</td>
<td>360,000,000</td>
<td>14,000,000</td>
</tr>
<tr>
<td>HCV</td>
<td>4,000,000</td>
<td>4,000,000,000</td>
<td>1,700,000</td>
</tr>
</tbody>
</table>

*HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus.
†From the National Institutes of Health.
Fig. 1. Hepatitis C genome codes for a single polyprotein precursor that is subsequently cut into individual proteins by host enzymes and the hepatitis C virus (HCV) protease. Lower boxes indicate positions corresponding to the four HCV protein fragments used in second-generation enzyme immunoassays and radioimmunoblot assays.

Extrahepatic Diseases
Chronic HCV infection may be associated with small-vessel vasculitis and is the most common cause of essential mixed cryoglobulinemia. Evidence of HCV infection should be sought in patients with cutaneous vasculitis, peripheral neuropathy, cerebritis, membranoproliferative glomerulonephritis, or nephrotic syndrome. At Mayo Clinic Rochester, approximately 20% of patients with sporadic porphyria cutanea tarda have HCV infection, and even higher percentages are reported in other parts of the world. Some patients with chronic hepatitis C have modestly increased levels of hepatic iron, and this may be the explanation for the association. The skin lesions seem to respond to iron removal therapy in most patients, but whether antiviral therapy has a role in the management of the skin disease is still unclear.

Diagnostic Techniques
As yet, no diagnostic tests are available for HCV viral proteins. Infection is diagnosed by testing for the patient’s antibody to HCV or testing directly for the virus RNA (or both). In screening for HCV infection, the blood is tested for anti-HCV antibody. This is not a protective antibody and does not confer immunity; in fact, it is present simultaneously with the virus and is a marker of infection, except in 15% of acutely infected people who have self-limited infections but may retain the antibody indefinitely.

Antibody Tests
Commercial kits for the antibody test are reliable, with a sensitivity of almost 95%. Initial antibody testing is performed with an enzyme immunosorbent assay that uses four target HCV protein fragments in solution with the patient’s serum (Fig. 1). If positive, the presence of antibody is confirmed with a radioimmunoblot assay (RIBA) that tests the patient’s serum against the same four HCV protein fragments attached to a strip; this approach has a greater specificity. If the patient’s serum reacts with two or more of the strips in the RIBA, the test result is positive; if it reacts with one strip, it is indeterminate. Truly infected patients may have indeterminate RIBA results, particularly those infected with less common HCV genotypes.

Confirming the specificity of a screening antibody test is important, especially in populations with a low background prevalence of HCV infection, such as asymptomatic blood donors. In contrast, a positive anti-HCV test result by enzyme immunosorbent assay is adequate for confirming infection in a high-risk patient who has evidence of chronic hepatitis. If anti-HCV antibody is confirmed by RIBA in a low-risk patient, a physician should seek evidence of liver disease by physical examination and determination of the serum ALT.

Tests for HCV RNA
Tests for HCV RNA are of two types, qualitative and quantitative. Qualitative RNA tests are designed to be very sensitive in order to determine whether any virus is in the blood. The most sensitive of these is the polymerase chain reaction (PCR) assay, in which even minute amounts of viral RNA can be amplified and then detected. The problem with PCR assays is that they are not standardized and may be unreliable. For example, a survey of 31 laborato-
ries that used a test panel of patient serum samples showed that only 16% were able to report all the results correctly. Quantitative RNA tests measure the level of viral RNA in the blood. They are useful in monitoring the patient’s response to treatment and may be helpful in making therapeutic decisions. (For example, a high RNA level may dissuade the physician and patient from pursuing treatment when the indication for treatment is otherwise borderline.) These tests are less sensitive than are qualitative PCR tests and should not be used for screening. The commercial test kits for RNA quantification, such as the branched DNA signal amplification assay, seem to be reliable from laboratory to laboratory, but quantitative PCR assays are likely to be unreliable unless performed rigorously by a major reference laboratory.

Genotyping

Although methods are available to determine virus genotype, the clinical utility of typing does not seem to be strong enough to warrant its use as a standard test at this time.

Liver Biopsy

Liver biopsy is the “gold standard” to determine grade (inflammatory severity) and stage (degree of fibrosis) of chronic hepatitis C. An inconsistent relationship exists between either the symptoms or the degree of liver enzyme abnormality and the severity of disease as judged histologically. The purpose of a liver biopsy is to (1) assess severity of disease in order to make a decision about treatment or (2) to determine the stage of disease, both for prognostic purposes and for diagnosing cirrhosis. Serial biopsy studies suggest that patients with mild chronic hepatitis and no fibrosis in the liver biopsy specimen have about a 50% risk of histologic progression of their disease over 10 years without treatment and perhaps a 10% risk for the development of cirrhosis, whereas those with severe hepatitis or septal fibrosis (or both) have a 60 to 70% risk for the development of cirrhosis during the same time frame.

TREATMENT

Rationale

For most patients, treatment is aimed at prevention of progression to future complications rather than relief of current symptoms. The primary goal is virus eradication, but this has not been achieved in five of six patients. A secondary goal is to reduce inflammation and liver cell damage (normalization of serum ALT and improvement in liver histology). Recent retrospective analyses have suggested that short-term interferon treatment may reduce the subsequent risk of hepatocellular cancer, but this has not been tested in prospective studies. Whether long-term reduction of viremia or suppression of inflammation slows progression of disease has likewise not been proved. Some patients with severe symptoms may feel better with treatment.

Interferon

Several types of interferon alfa have been evaluated in the treatment of patients with chronic hepatitis C. Recombinant interferon alfa-2b was originally licensed in the United States for 6 months of treatment at 3 million U administered subcutaneously three times a week; thus, the vast majority of information pertains to this regimen. Treatment for up to 24 months is now possible, however. Increasing the duration of treatment does not increase the initial response rate, but it decreases the number of relapses and consequently increases the sustained virus disappearance rate to 20 to 30%. Recombinant interferon alfa-2a is licensed for 12 months of treatment, and “consensus” interferon (a synthetic interferon representing a consensus sequence from a number of naturally occurring interferons) is approved for 6 months of treatment. These three products have essentially equal clinical efficacy. Other interferons have been tested (lymphoblastoid, beta, and natural), but all seem to have efficacy similar to that of the currently licensed products.

Recommendations

Treatment is recommended for patients whose disease is most likely to progress to cirrhosis—those with persistent increases of the serum ALT level, presence of HCV RNA in the blood, and a biopsy specimen showing moderately severe hepatitis or some degree of fibrosis (or both). Therapy should be initiated at a dose equivalent to interferon alfa, 3 million U three times weekly, with the intent to treat for 12 months. The therapeutic benefit is less clear in patients with mild hepatitis or cirrhosis and in those older than 60 years of age and thus must be judged individually. In view of their generally good prognosis, patients with mild biochemical and histologic hepatitis may elect to undergo observation without treatment; however, a liver biopsy should be repeated in 3 to 5 years, and treatment should be strongly considered if histologic progression is evident. Ironically, these patients are most likely to respond to treatment.

Response

Response to treatment, as measured by the serum ALT level, occurs in 40 to 50% of patients by the end of 6 months of therapy, but in most patients, disease recurs after treatment is discontinued; thus, the sustained response rate (determined at least 6 months after withdrawal of therapy) is only 15 to 20%. If the more rigorous standard of
HCV RNA disappearance is used, the response rate at the end of treatment is 30 to 40%, and the sustained response rate is only 10 to 15%. After 12 weeks of treatment, if the serum remains positive for HCV RNA, the likelihood of a subsequent response is extremely low, and treatment should be discontinued. The factors most closely associated with a response to treatment are absence of cirrhosis in a liver biopsy specimen, low serum HCV RNA level (less than 1 million viruses/mL), and HCV genotype other than type 1. None of these, however, should be used categorically to exclude a patient from treatment.

Adverse Effects

Adverse effects of interferon therapy occur in most patients, but only 5% need to discontinue treatment. Within a few hours after injection, most patients develop influenza-like symptoms consisting of headache, fever, chills, muscle aches, and malaise, but such symptoms usually disappear after the first few doses and are substantially diminished by the third or fourth week. Bone marrow suppression, particularly thrombocytopenia and leukopenia, can occur early or late after initiation of treatment, and a complete blood cell count must be performed at 1, 2, and 4 weeks and then monthly; this condition reverses with dose reduction or discontinuation of the drug. Long-term effects include fatigue (40%) and emotional disturbances such as irritability and depression (25 to 30%). Hair thinning is common (20%), but frank alopecia has not been reported. Thyroid dysfunction is induced in about 5% of patients, and usually hormone replacement therapy is needed. Rare adverse effects include retinopathy, suicidal depression, and acute cardiac failure.

Contraindications

Interferon treatment is contraindicated in patients with cytopenias (for example, leukocyte count less than 3 x 10^9/L or platelet count less than 75 x 10^9/L), severe depression, and autoimmune disease because the preexisting condition may be aggravated. Treatment is contraindicated in patients with active thyroid disease; however, those who are receiving treatment for hypothyroidism and who have a normal sensitive thyroid-stimulating hormone level can receive interferon treatment. The immediate adverse effects of treatment may not be safely tolerated by those with active drug or alcohol abuse. Patients who have undergone transplantation have a risk of precipitating rejection.

Cost-Effectiveness

In the absence of definitive evidence from prospective studies that interferon treatment prolongs life or enhances the quality of life, the theoretical potential benefit from interferon therapy has been estimated by using computer simulation models. Such models use the literature and expert opinion to assign probabilities to various outcomes in order to estimate survival and cost-effectiveness. The conclusions drawn from these models are only as accurate as the assumptions on which they are based. Using such a model, we estimated that the cost of 6 months of interferon therapy was $2,800 per quality-adjusted year of life gained for patients 40 years old and $11,100 for patients 60 years old. With use of the model, the corresponding figures for 12 months of treatment were $3,700 and $12,800, but a larger absolute number of patients received benefit. In general, the US public has accepted strategies in which the cost per year of life gained is about $50,000 or less—for example, screening mammography, coronary artery bypass grafting, or renal dialysis. Of note, the cost-effectiveness of the last-mentioned procedures has been established in prospective studies.

Combination Therapy

Combination therapy with interferon and ribavirin has recently shown promise of improving results. Ribavirin is an orally administered nucleoside analogue that, by itself, has a suppressive effect on disease activity in chronic hepatitis C but no effect on HCV viremia. In early 6-month clinical trials from various parts of the world, combination therapy has increased the sustained virus disappearance rate to 40 to 50% in previously untreated patients. A recent unpublished multicenter study of 350 patients showed that combination treatment may be particularly effective in the re-treatment of those whose disease recurs after an initial response to interferon monotherapy. Patients were randomized to receive re-treatment with 6 months of interferon alfa-2b, 3 million U three times weekly, or re-treatment with the same schedule of interferon plus ribavirin daily. The difference in outcomes 6 months after the end of re-treatment was substantial—a sustained disappearance of viremia in 47% of the combination group but only 5% of the interferon monotherapy group. Patients taking ribavirin usually experience some degree of reversible hemolytic anemia, and 15% will have a decrease in the hemoglobin concentration of 4 g/dL or more, a particularly hazardous effect in patients with pre-existing or underlying heart disease.

Future Therapies

The development of new treatments for chronic hepatitis C has been hampered by the lack of a dependable cell culture system, the lack of a small animal model of the disease, and the relative lack of research funding. The serine protease of the virus was recently purified and its three-dimensional structure elucidated, leading us to ex-
pect the development of HCV-specific protease inhibitors in the next decade. Other experimental approaches to treatment have included HCV-specific antisense oligonucleotides, virus-specific ribozymes, and immunomodulation with cytokines, but all these approaches seem to be far from clinical application.

GENERAL RECOMMENDATIONS

Advice to Patients

Patients with chronic hepatitis C often ask for general advice about long-term care of their disease. They should abstain from using alcohol because no studies have clearly shown whether any level of alcohol use is safe. No other specific dietary changes are necessary, except those designed to achieve good general health. If not limited by another medical condition, patients should be encouraged to start a regular low-level aerobic exercise routine. Vaccination against hepatitis viruses A and B should be performed if natural immunity is not present. Patients receiving treatment should undergo an examination every 6 months. Patients with precirrhotic disease who have not responded to treatment or who are not candidates for treatment should be examined by a physician once a year. Those with cirrhosis should be examined every 6 months.

Referral of Patients

Experienced primary-care physicians who follow up patients with chronic hepatitis C may be comfortable prescribing and monitoring interferon therapy, but others may choose to refer the patient to a specialist. Patients in whom initial therapy has failed and who are interested in further treatment possibilities should see a specialist. Those who have cirrhosis and a reduced quality of life or occurrence of a decompenetration event should be followed up by a specialist and, if appropriate, be referred for consideration of liver transplantation.

PREVENTION

Prophylaxis with immune serum globulin after a patient has been exposed to HCV infection is not effective; however, in the setting of acute HCV infection, treatment with interferon reduces the rate of chronic infection. Prophylaxis with an early version of an HCV vaccine before exposure to HCV infection was tested in chimpanzees but was only partially effective. Development of a vaccine has been difficult because of the high mutation rate of the virus. In the meantime, prophylaxis before exposure continues to depend on preventing transmission from infected persons. On the basis of existing Public Health Service guidelines,12 the National Institutes of Health Consensus Development Conference recently made the following recommendations to prevent transmission of hepatitis C:

1. Universal infection precautions should be used in health-care settings.
2. Infected persons should not ordinarily donate blood, tissues, body organs, or semen. Infected organs might be considered in urgent lifesaving situations.
3. Infected persons with multiple sexual partners should use barrier protection such as condoms. In monogamous long-term relationships, no changes in sexual practices are necessary.
4. Sexual partners of infected persons should be tested for anti-HCV antibody.
5. In a household with an infected member, sharing of toothbrushes and razors should be avoided. Avoiding close contact is unnecessary.
6. Pregnancy is not contraindicated in infected women. Breastfeeding is safe and should be encouraged.
7. Needle-exchange programs are of proven benefit and should be expanded. (This last point was the opinion of the consensus panel and may be a politically controversial issue despite the fact that it makes sense from an epidemiologic point of view.)

ACKNOWLEDGMENT

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Questions About Hepatitis C
(See article, pages 355 to 360)

1. Which one of the following is true of hepatitis C infection?
   a. It is more easily transmitted than is hepatitis B or human immunodeficiency virus (HIV)
   b. It has a high rate of fulminant liver failure
   c. It frequently causes chronic asymptomatic infection
   d. Drug development research has been more expensive than that for HIV
   e. No long-term responses to medical therapy are available

2. Which one of the following groups has the highest prevalence of hepatitis C virus (HCV) infection?
   a. Patients assessed in inner-city emergency departments
   b. Infants of HCV-infected mothers
   c. Long-term sexual partners of HCV-infected persons
   d. Health-care workers
   e. Homosexual men

3. Which one of the following is probably the least important in contributing to the development of fibrosis in chronic hepatitis C?
   a. Duration of infection
   b. Male sex
   c. Level of alcohol consumption
   d. Level of viremia
   e. Age at onset of infection

4. A 42-year-old woman is discovered to be anti-HCV positive by enzyme immunoassay during blood donation screening, and this is confirmed by radioimmunoblot assay (RIBA) testing. Which one of the following is the next step?
   a. Qualitative testing for HCV RNA by polymerase chain reaction
   b. Determination of serum alanine aminotransferase (ALT) and performance of liver biopsy
   c. Screening for cancer by ultrasonography and level of alpha-fetoprotein
   d. Quantitative testing for HCV RNA by branched DNA assay
   e. Performance of physical examination and determination of serum ALT

5. A 37-year-old man was found to have serologic and histologic evidence of mild chronic hepatitis C. After 6 months of treatment with interferon alfa, 3 million U three times weekly, the serum HCV RNA was negative, and the ALT was normal. He had recurrence of disease 2 months later. Which one of the following is the best choice for this patient?
   a. Observation until more effective therapy becomes available
   b. Re-treatment with interferon plus ribavirin
   c. Re-treatment with a higher dose of interferon for 6 months
   d. Re-treatment with the same dose of interferon for 1 year
   e. Performance of another liver biopsy to assess histologic progression

Correct answers:
1. c, 2. a, 3. d, 4. e, 5. b