

Under the Radar: Why Hepatitis C Is So Hard to Control

Viral hepatitis has been, if not a faithful, at least a constant companion of humans for at least 2000 years.¹ By 1974, both hepatitis A and hepatitis B had been identified; for the next 15 years, a mysterious variant was known as *non-A, non-B hepatitis*, and, when identified, hepatitis C accounted for the vast majority of those. In fact, when hepatitis C virus (HCV) was identified in 1989, it seemed to explode in almost epidemic proportions, having been spread unwittingly for decades by blood transfusions and illicit parenteral drug use. Now it is the most common blood-borne infection in the United States.²

Epidemiology

Nearly 4 million people in the United States, or 1 of every 50 adults, are infected with HCV.³ It is estimated that about 20% of those whose HCV is chronic develop cirrhosis, and people with cirrhosis from HCV develop liver cancer at a rate of 1% to 4% per year. In the developed world, almost half of all instances of primary liver cancer are preceded by HCV, and HCV is now the most common indication for liver transplants.⁴ As many as three quarters of those infected with HCV are thought to be undiagnosed. Those unaware of their condition can neither be advised of early risk reductions related to alcohol use and weight reduction nor prescribed medication to treat the disease.

The frequency of new HCV infections is now remarkably reduced, thanks in large part to information that changed the habits of high-risk people and screening of donated blood.⁴ But intravenous drug users, the incarcerated, and the homeless remain at high risk, and, in some other areas of the world, transmission of HCV through blood transfusions is still high. Nosocomial transmission of HCV through such practices as sharing single-use vials for infusions contributes to a generally higher rate of HCV infection worldwide.⁵

Virology

Hepatitis C, a ribonucleic acid (RNA) virus of the family Flaviviridae, has at least 6 genotypes and numerous subtypes.⁶ This extensive genetic heterogeneity and a high viral propensity to mutate make it difficult to develop a viable vaccine. Genotype is not a factor in the natural history of the disease

but does influence treatment response and, therefore, length of therapy. In the United States, about 70% of people with HCV have genotype 1, the most difficult to treat. Genotype 1b is predominant in Chile and Japan. The Indian subcontinent reveals a predominance of genotype 3 among the HCV infected, while the Middle East and Africa have higher percentages of genotype 4.^{5,7} Genotype 5 is predominant in South Africa and genotype 6 in Southeast Asia.⁵

HCV infects only humans and chimpanzees,⁸ is spread by blood-to-blood contact, and can be detected in blood as soon as 1 to 3 weeks after initial exposure. Injury to liver cells is detected by elevated serum alanine aminotransferase (ALT) levels within an average of 4 to 12 weeks after infection, while it is still in its acute phase. Typical symptoms of hepatitis, such as malaise, weakness, anorexia, and jaundice, are uncommon, but if present will usually subside as ALT levels decline. The infection is more likely to clear spontaneously in people of younger age and in those with certain major histocompatibility-complex genes.

Up to 85% of patients acquiring hepatitis C remain chronically infected. Untreated, progressive liver fibrosis resulting from chronic HCV can lead to cirrhosis and premature death from complications of end-stage liver disease and hepatocellular carcinoma (HCC).⁶ In the United States, cirrhosis that results from hepatitis C is the reason for almost 50% of liver transplants; worldwide, the virus is a significant economic burden on healthcare resources.

Natural History

Progression of HCV infection is slow, and the time it takes for cirrhosis to develop appears to fall between 20 and 30 years. Virologic factors such as viral load and genotype do not affect the rate of liver disease progression. Factors likely to influence the rate of progression to cirrhosis in those chronically infected include male sex, age older than 40 years at infection, more than 30 g of alcohol ingested daily, and coinfection with either human immunodeficiency virus or hepatitis B virus; more recent data indicate that diabetes and obesity are risks for faster disease progression as well.

When chronic HCV infection has progressed to cirrhosis, subsequent complications can produce hepatic decompen-

sation, manifested by complications such as ascites, esophageal variceal bleeding, or hepatic encephalopathy.⁷

Screening

It is not reasonable to attempt to screen all asymptomatic adults with a low probability of HCV infection. Routine screening needs to be confined to those with higher risk. The population of adults who do have risk factors is not small; it includes anyone who received blood products or transplanted organs before 1992, when donor screening for HCV began; people with hemophilia who received coagulation factors before 1987; people with any history of injectable drug use; patients receiving long-term hemodialysis; and immigrants from countries in which the prevalence of HCV infection is high. Also at higher risk are infants born to mothers with HCV.^{4,7} If clinical or biochemical evidence of liver disease is detected, patients should receive HCV serologic testing, as should spouses of people with chronic HCV. Routine screening consists primarily of serologic testing for antibodies to hepatitis C (anti-HCV).

Serologic Testing. Enzyme-linked immunosorbent assay (ELISA) tests, the first line in diagnosis, detect antibodies to HCV in plasma or serum.^{7,9} Anti-HCV remains positive even in those who have cleared the infection spontaneously or with treatment. The current third-generation ELISAs have a 99% sensitivity and specificity as soon as 7 or 8 weeks after infection.⁷

Molecular Testing. Those who test positive for anti-HCV can have their viremia levels measured by HCV RNA testing. HCV RNA levels are measured by highly sensitive reverse transcription polymerase chain reaction tests, which are useful to confirm HCV infection and are also used to evaluate response to antiviral therapy during treatment. HCV RNA, which can be measured quantitatively or qualitatively, can be detected as soon as 1 or 2 weeks postinfection. In cases of acute infection, HCV RNA becomes positive before the appearance of anti-HCV.⁷

Genotype Testing. Once infection is confirmed, HCV genotype (1 to 6) is determined with enzyme

immunoassay antibodies for genotype-specific HCV epitopes, sites against which antibodies will be produced and to which they will bind.⁹ Determination of HCV subtype involves direct sequencing of specific regions of the viral genome.^{6,9}

Liver Biopsy. Diagnosis of HCV infection is confirmed by virologic testing of HCV RNA. Liver biopsy is useful, especially in cases of genotype 1 infection, to determine stage or assess the extent of liver injury before treatment, as well as to guide treatment.^{7,9} Patients for whom biopsy reveals cirrhosis should undergo surveillance for HCC and esophageal varices. Liver biopsy can assist in selection of patients for treatment and in providing prognosis. In some cases, liver biopsy serves to reassure patients that their disease is mild. Patients whose liver biopsy reveals mild chronic disease can consider the alternative of postponing treatment for a few years, with monitoring, particularly if they have comorbidities. Hepatic steatosis, which is not uncommon in those infected with HCV, can also be identified through liver biopsy.⁷

Diagnosis

By the time any symptoms of HCV infection show, the disease may be well advanced. Therefore, recognition of people likely to be harboring hepatitis C is greatly dependent on accurate risk assessment by healthcare workers.

Acute Hepatitis C. It is rare for clinicians to see patients with acute hepatitis C. When acute hepatitis C is recognized, treatment is often administered because of a high rate of response, although some have advised a “wait and see” approach to determine if spontaneous clearance occurs.

Because of the paucity of recognized cases of acute hepatitis C, the optimal treatment regimen, dose, time to begin therapy, and length of treatment have not been established for acute HCV infection. A conservative course would be starting therapy 2 to 3 months after diagnosis of acute infection and extending treatment for at least 24 weeks.

If both HCV RNA and anti-HCV are lacking, or if anti-HCV is found without HCV RNA, acute hepatitis C is unlikely. Retesting in a few weeks, however, is advised, because viral levels can (rarely)

Introduction

temporarily decrease below the lower level of detection of assays.⁹

Chronic Hepatitis C. Chronic hepatitis C is diagnosed unequivocally in patients with clinical or biological signs of liver disease when HCV RNA and anti-HCV are present. Although extremely rare, when HCV replication without anti-HCV is found, the patient is almost always intensely immunosuppressed, agammaglobulinemic, or receiving hemodialysis.⁹ Patients with chronic HCV may have various intermittent, nonspecific symptoms—fatigue, asthenia, abdominal discomfort—that do not correlate with severity of disease and are not in themselves a sufficient indication for treatment.¹⁰ Many patients will have elevated ALT levels, which do not correlate with disease severity and are not a prerequisite to treatment. Before engaging in treatment, patients need to understand that they must be compliant, although treatment may be accompanied by considerable side effects.

Once the diagnosis of HCV is made, vaccination for hepatitis A and B is advised for those who lack immunity to these agents.

Conclusion

HCV infection is a widespread, elusive disease that can progress for decades without detection. By the time symptoms appear, there is a major health and

medical problem. Public education and screening of high-risk populations are crucial to gaining control of this quiet but destructive, often fatal illness.

REFERENCES

1. **Dharmananda S.** Hepatitis C: recent treatment strategies. September 1998. www.itmonline.org/arts/hepcstrat.htm. Accessed October 31, 2007.
2. **National Institute on Drug Abuse.** Facts About Drug Abuse and Hepatitis C. March 2000. www.nida.nih.gov/NIDA_Notes/NNVol15N1/tearoff.html. Accessed October 2, 2007.
3. **National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention.** National Hepatitis C Prevention Strategy: Hepatitis C Infection in the United States. www.cdc.gov/Ncidod/diseases/hepatitis/c/plan/HCV_infection.htm. Accessed October 31, 2007.
4. **Dienstag JL, McHutchison JG.** American Gastroenterological Association medical position statement on the management of hepatitis C. *Gastroenterology*. 2006;130:225-230.
5. **Sy T, Jamal MM.** Epidemiology of hepatitis C virus (HCV) infection. *Int J Med Sci*. 2006;3:41-46.
6. **NIH.** Management of hepatitis C: 2002. National Institutes of Health, 2002. consensus.nih.gov/PREVIOUS STATEMENTS.htm. Accessed November 1, 2007.
7. **Huang RH, Hu KQ.** A practical approach to managing patients with HCV infection. *Int J Med Sci*. 2006;3:63-68.
8. **Hepatitis C awareness project.** National HCV Prison Coalition. www.hcvinprison.org/new/about_hcv.html. Accessed September 23, 2007.
9. **Chevaliez S, Pawlotsky JM.** Hepatitis C virus serologic and virologic tests and clinical diagnosis of HCV-related liver disease. *Int J Med Sci*. 2006;3:35-40.
10. **Patel K, McHutchison JG.** Current therapies for chronic hepatitis C. *Postgrad Med*. 2003;114:48-52,57-59,62.