

Appropriate Screening and Early Diagnosis of Hepatitis B and C

Based on a presentation by David R. Gretch, MD, PhD

Presentation Summary

Many patients infected with hepatitis B virus (HBV) or hepatitis C virus (HCV) experience no outward symptoms, remaining fairly healthy yet able to infect other people. The asymptomatic nature of chronic viral hepatitis underscores the importance of screening tests for HBV and HCV. For HCV infection, enzyme-linked immunosorbent assay (ELISA) is the most practical means of screening patients. However, this antibody screening test can produce false-positive results, particularly in patients at low risk for HCV infection. The recombinant immunoblot assay (RIBA), a more sophisticated test, is used to supplement the ELISA in low-risk patients with false-positive test results but is not cost effective in

high-risk patients. When a false-negative result is suspected in patients at high risk for HCV infection, polymerase chain reaction (PCR) can be used to directly detect virus in blood. Serologic screening tests also are used to identify patients infected with HBV. The hepatitis B surface antigen (HBsAg) screen is particularly important, since a positive result indicates that patients' blood and organs are potentially infectious. By screening high-risk pregnant women for HBsAg, clinicians can identify those most likely to transmit the infection to their newborns and institute appropriate therapy. Viral load testing can help clinicians implement optimal antiviral therapy for HCV infection.

The importance of screening tests for chronic hepatitis B and C is illustrated by the asymptomatic nature of the disease. Nearly 5 million individuals in the United States have chronic hepatitis B or C,^{1,2} many of whom are unaware they harbor the virus. Of the 150,000 new cases of hepatitis C reported in 1995, between 60% and 70% were asymptomatic in their initial presentation.^{3,4} Identifying these patients and imple-

menting early treatment may help prevent progression to chronic liver disease or cirrhosis.

Screening and Diagnostic Tests for Hepatitis C

"Hepatitis C is virologically much more like human immunodeficiency virus (HIV) infection than any other viral infection. About 85% of people infected with hepatitis C will have the virus persistently present in their

blood for the rest of their life," said Dr. Gretch. "This is an important point when discussing screening tests." Several tests are available for screening and diagnosing patients and assessing the effectiveness of antiviral therapy (see Table 1).

The enzyme-linked immunosorbent assay (ELISA) detects antibodies to hepatitis C virus (HCV), which is the most practical means of diagnosing both past and present infection.⁵ With ELISA, antigens (proteins) from the virus are cloned and coated onto beads or a microwave plate. If antibodies to HCV are present in the patient's blood, they bind to the antigens. These bound antibodies can then be detected in the laboratory. A positive ELISA test may indicate an active HCV infection, a past infection that has resolved, or a false-positive result. False-positive results, even with third-generation ELISA tests, are seen among low-risk populations, such as blood donors.⁵ "However, in high-risk groups, such as

injection drug users, patients who have received blood transfusions, and patients with abnormal liver enzyme levels, the ELISA test is more than 99% specific," noted Dr. Gretch.

Supplemental testing with a recombinant immunoblot assay (RIBA) is indicated for people at low risk for HCV infection who test positive on the ELISA. Similar to the Western blot test, RIBA contains four HCV-specific antigens blotted as separate bands on a nitrocellulose strip.⁶ Reactions between antibodies (if present) in patients' blood and the HCV antigens can then be visually detected.

Although second- and third-generation ELISA and RIBA tests are highly sensitive, up to 5% of patients infected with HCV have false-negative tests for antibodies.⁶ In some cases, false-negative results occur because patients are tested before seroconversion (development of antibodies). The median time to seroconversion after exposure to HCV is about 8 weeks but can be as long as 1 year.²⁴ False-negative results also occur among immunocompromised patients, such as transplant recipients, hemodialysis patients, and HIV-positive patients. In some patients, antibody levels are so low they cannot be detected by currently available ELISA and RIBA tests. For patients at risk for HCV with false-negative antibody screening tests, polymerase chain reaction (PCR) can be used to detect HCV directly in the blood.

"The PCR tests are widely used for diagnosing active hepatitis C, active hepatitis B, and HIV infection," said Dr. Gretch. "With these tests, we can determine not only whether virus is present in the blood but also measure the amount. Being able to quantify the amount of virus helps clinicians evaluate antiviral therapy for HCV." In explaining the PCR process, Dr. Gretch likened it to a molecular copying

Table 1. Screening and Diagnostic Tests for Hepatitis C Virus (HCV)

Type of Test	Method	Use
Enzyme-linked immunosorbent assay (ELISA)	Detects antibodies to HCV	Initial screening and diagnosis
Recombinant immunoblot assay (RIBA)	Detects antibodies to HCV	Supplemental testing for low-risk patients with positive ELISA results
Polymerase chain reaction (PCR)	Detects HCV RNA	Confirmation of active HCV infection (HCV viremia - detection of early infection)
Viral load testing	Quantifies HCV*	Predicting response to and evaluating effectiveness of antiviral therapy
Genotype testing	Identifies HCV genotype*	Predicting response to and evaluating effectiveness of antiviral therapy

*Research applications only.

machine. Viral RNA is extracted from the virus, converted to cDNA by reverse-transcriptase activity, then amplified by PCR.⁶ "For every copy of virus, the PCR 'copying machine' can make approximately 10⁶, or about 1 million, copies of an amplified product," explained Dr. Gretch. "Through this copying process, we can reach a level high enough to detect the virus with radioactive probes." Since no commercially produced assays currently are available for detecting HCV,⁶ lack of standardization is the greatest problem with PCR testing. Ideally, laboratories should have an ongoing method for testing their proficiency and participate in the College of American Pathology Proficiency Testing for Hepatitis C.

Additional tests are available to help clinicians make optimal use of antiviral therapy. Measures of viral load are useful for predicting response to specific therapeutic regimens and for tracking response to therapy. "Because viral load is a relatively constant aspect of hepatitis C, we can stratify patients according to their viral load—either low, intermediate, or high," elaborated Dr. Gretch. "In the research setting, HCV viral load has predictive value in terms of who will respond rapidly to interferon and who might need a more aggressive course. If clinicians use the same viral load test to follow a patient, they can draw clear conclusions about the effect of therapy on viral load." However, HCV viral load testing has not been approved by the Food and Drug Administration (FDA) and is therefore a research test.

Identifying the specific HCV genotype can be useful in predicting response to antiviral ther-

apy and may possibly prove valuable in predicting disease severity, likelihood of progression to cirrhosis, and outcome of liver transplantation.⁶ At least six different HCV genotypes have been identified worldwide. "We have multiple tests that can determine the genotype, and some of these tests are now available in easy-to-use kits," noted Dr. Gretch. "Many reference laboratories now offer genotype testing." HCV genotype determination is important for research studies. However, the value of HCV genotype testing in routine patient care remains to be shown.*

Screening and Diagnostic Tests for Hepatitis B

"Hepatitis B virus (HBV) to some degree is easier than HCV to test in the laboratory, even though this virus has a sophisticated life cycle and replicates like a retrovirus," said Dr. Gretch. Tests are available to detect HBV and the various antigens and antibodies made in response to HBV infection (see Table 2).

Table 2. Screening and Diagnostic Tests for Hepatitis B Virus (HBV)

Type of Test	Method	Use
Hepatitis B surface antigen (HBsAg)	Detects HBsAg	Screening blood products, organ donors, pregnant women, and patients at risk for hepatitis
Hepatitis B e antigen (HBeAg)	Detects HBeAg	Indicating high infectivity and ongoing infection ELISA results
Hepatitis B anticore antibody	Detects antibody to HBV core protein	Determining past exposure to HBV
Hepatitis B anti-surface antigen antibody	Detects antibody to HBV surface antigen	Indicating resolution of infection or successful vaccination with HBsAg
PCR	Detects HBV DNA	Indicating active HBV infection, useful for therapeutic management

*NOTE: The clinical importance of detecting genotype 2 and 3 will be published this year.

Hepatitis B surface antigen (HBsAg) is the initial marker of HBV infection. In most unvaccinated adults, the infection resolves and patients become immune. In less than 5% of patients, HBsAg persists after the acute infection, and antibodies to HBsAg do not develop; these patients become carriers of the virus and are likely to develop chronic hepatitis.²

The best marker of infectivity is the hepatitis B e antigen (HBeAg), the presence of which indicates that a patient's blood and organs are highly infectious. Patients with chronic hepatitis B who test negative for HBeAg usually can also transmit the disease to others. Thus, HBeAg negativity does not guarantee lack of infectivity. Infants born to women who test positive for HBsAg usually are infected at birth, become carriers for life, and often have a poor long-term prognosis. By screening pregnant women for the presence of HBsAg, clinicians can identify those who are carriers and take measures to prevent chronic infection in their newborns.

Conclusion

With the morbidity and mortality from HBV and HCV infection potentially reaching epidemic proportions in

the United States, screening for the viruses is crucial. Screening can be accomplished through patient questionnaires, review of patient histories, and serologic testing of patients at high risk and those with abnormal liver enzymes. Antiviral treatment of patients infected with HBV or HCV may prevent further complications that are costly to treat and reduce life expectancy and quality.

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