HEPATITIS C VIRUS (HCV) is a single-stranded, positive sense RNA virus with a genome of approximately 10,000 nucleotides coding for 3,000 amino acids. The virus is the principle etiologic agent responsible for more than 90% of posttransfusion non-A, non-B hepatitis. The global prevalence of HCV infection, as determined by immunoserology, ranges from 0.6% in Canada, 1.5% in Japan, to 6% in Africa. Although generally asymptomatic, about 85% of the infections become chronic. Persistent HCV infection may be associated with a wide spectrum of outcomes, from mild nonprogressive liver damage to severe chronic hepatitis that progresses to cirrhosis, end-stage liver disease, and hepatocellular carcinoma.

Prevalence of HCV infection is high in patients undergoing renal dialysis or receiving organ transplants. Approximately 10% of chronic hemodialysis patients in the United States have chronic HCV infection. However, prevalence of infection varies widely from center to center. The high incidence and prevalence of HCV infection among dialysis patients can be attributed to several risk factors, including blood transfusion, duration of dialysis, mode of dialysis (lower risk with peritoneal dialysis), and a history of previous organ transplantation or intravenous drug abuse. Nonetheless, a national survey conducted by the Centers for Disease Control and Prevention (CDC) showed that only 56% of dialysis centers in the United States test their patients for HCV infection despite the CDC’s recommendation for routine testing of patients not previously evaluated for HCV infection. The CDC currently advises screening chronic hemodialysis patients for HCV infection by serial alanine aminotransferase (ALT) measurements. Patients identified by elevated ALT levels should then undergo additional immunoserologic testing for antibody against HCV (anti-HCV). Reasons offered for failure to test for HCV infection include (1) that HCV is thought to be less infectious than hepatitis B infection, (2) that anti-HCV tests do not distinguish between current and past infection, (3) the high incidence of false-positive anti-HCV by enzyme-linked immunosorbent assay (ELISA), (4) the subsequent need of additional confirmatory tests (eg, HCV RNA), and (5) that anti-HCV tests may be negative in the initial period before seroconversion.

In this issue of the Journal, Saab et al examine the cost-effectiveness of a screening strategy based on ALT values as currently recommended by the CDC compared with other potential screening strategies. Under baseline assumptions using a decision analysis model of a simulated cohort of 5,000 hemodialysis patients followed for 5 years, the estimated per patient cost of screening hemodialysis patients for HCV was $378 for biochemical-based testing (ALT plus anti-HCV testing), $195 for serological-based testing (anti-HCV testing), and $696 for viral-based testing (HCV RNA). The authors conclude that serological-based screening is less costly and more effective than biochemical-based screening in the diagnosis of de novo HCV infection. This study casts doubt on the current CDC recommendation in using ALT testing for HCV surveillance in hemodialysis patients. If serological-based screening were considered for HCV screening in hemodialysis centers, what would be the potential benefits and limitations? In addition, what is the role of viral-based testing?

Obviously, ALT is not a sensitive screening test for HCV infection in uremic subjects, as most uremic patients with HCV infections have normal ALT values. Because baseline ALT values are frequently lower in hemodialysis patients than in nonuremic patients, the “elevated” ALT values in hemodialysis patients who are viremic with HCV may still fall within the normal reference range for nonuremic subjects. Furthermore, nonspecific sporadic elevations of ALT are common in hemodialysis patients due to other comorbidities and medications. Thus, screening for HCV infection in these patients requires sensitive and specific serological testing.

The most commonly used assay for anti-HCV

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is the enzyme immunoassay (EIA), in which viral antigens are imbedded in the wells of a microtiter plate. Three generations of EIA for anti-HCV have been developed over the past decade. The first EIA (EIA-1) contained a single recombinant antigen from the NS4 region of the HCV genome. Its limitations are high false-positive reactions with low sensitivity (70%). The second-generation EIA for HCV (EIA-2) contains antigens from the core and nonstructural regions (NS3 and NS4) of the HCV genome. EIA-2 has improved sensitivity (92%) and reduced false-positive reactions. A third-generation EIA (EIA-3) contains reconfigured core and NS3 antigens and an additional antigen from the NS5 regions of the HCV genome. This test offers a slight improvement in sensitivity over EIA-2. The time from infection to anti-HCV seroconversion is shortened to 7 to 8 weeks, as compared with 12 weeks in EIA-2 and 16 weeks in EIA-3. Because of the high false-positive rate of EIA tests, strip immunoblot assays (SIA) were developed as confirmatory tests. These tests contain the same antigens as the corresponding EIA assay. These tests contain the same antigens as the corresponding EIA assay. Individual HCV antigens are displayed on a nitrocellulose strip, and antibodies against specific HCV antigens can be identified. These tests are more expensive than EIA. They have limited usefulness among patients clinically suspected of harboring a chronic HCV infection in which case a viral-based testing is needed.

HCV RNA testing is essential for confirmation of active HCV infection and for monitoring of antiviral therapy. Following transplantation, antibody tests are inadequate for the diagnosis of HCV because of depression of antibody titers and prolonged delay in seroconversion after de novo infection. The only means of accurately assessing the presence of hepatitis C in transplant recipients is the direct measurement of HCV RNA. Both qualitative and quantitative tests for HCV RNA have been developed recently. Qualitative detection using reverse transcription-polymerase chain reaction (RT-PCR) under optimal conditions (rapid separation and storage of serum at −70°C) achieves a sensitivity of 100 molecules/mL of serum or less. Extreme care and high standards must be maintained to avoid a false-positive or negative result. Well-trained technologists are required and all runs need negative controls and multiple low and high copy standards to achieve maximum sensitivity and specificity of the RNA assay. Manual and semiautomated qualitative PCR assays with a sensitivity of approximately 100 copies/mL of serum are now available and are awaiting FDA approval. A variety of methods is available for assessing the quantity of serum HCV RNA levels in patients with HCV infection. The most commonly used methods involve extraction of HCV RNA followed by amplification of the target (PCR-based technique) or the signal (branched DNA [bDNA] technique). The sensitivities are lower than qualitative PCR assays, with 1,000 copies/mL in the PCR-based technique and 200,000 equivalents of HCV RNA/mL in the bDNA technique.

The latest breakthrough in diagnosing early HCV infection is by detecting the HCV core antigen (HCVcAg) that is present during the early stage of infection when anti-HCV antibodies have not been produced. A highly sensitive EIA for HCVcAg has been developed. There is a positive correlation between the concentration of HCVcAg and HCV RNA in anti-HCV antibody negative specimens. The EIA for HCVcAg is simpler than assays for HCV RNA based on gene technology and shows specificity, sensitivity, and a window period equivalent to those of commercial manual qualitative PCR assays. Thus, EIA for HCVcAg would be useful in screening asymptomatic HCV carriers or de novo infection in patients on renal replacement program and could reduce the residual risk of HCV infection in the hemodialysis unit.

**EPILOGUE**

When I finished writing this editorial at the end of April 2000, a new recommendation for preventing transmission of infection among chronic hemodialysis patients was released by CDC on April 27, 2001. CDC states that the only FDA-approved tests for diagnosis of HCV infection are those that measure anti-HCV and include EIAs and a supplemental SIA (RIBA). The diagnosis of HCV infection also can be made by qualitatively detecting HCV RNA using gene amplification techniques, although this is not FDA-approved (eg, RT-PCR). Quantitative
assays for measuring the concentration of HCV RNA are not FDA-approved and are less sensitive than qualitative RT-PCR assays.

Most interesting, the latest CDC report recommends routine HCV testing by both an EIA to test for anti-HCV and supplemental or confirmatory testing with an additional, more specific SIA. CDC does not recommend the use of RT-PCR for HCV RNA as the primary test for routine screening. However, if ALT levels are persistently abnormal in patients who are anti-HCV negative in the absence of another etiology, testing for HCV RNA should then be considered.

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