

## Hepatitis C—Removing Barriers to Diagnosing the “Silent Epidemic”

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Hepatitis C, caused by infection with the hepatitis C virus (HCV),<sup>3</sup> is the most common life-threatening chronic infectious disease in the US. According to a recent Institute of Medicine (IOM) report, between  $2.7 \times 10^6$  and  $3.9 \times 10^6$  people are chronically infected with HCV, and 75% of them are unaware of this infection (1). That finding led to the description of hepatitis C infection as a “silent epidemic” (2). Projections are that, without treatment, almost half of those infected will develop cirrhosis over the next 20 years, with almost 14 000 cases of hepatocellular carcinoma developing in HCV-infected individuals in the peak year of 2019 (3). Treatment with the drugs currently available leads to eradication of detectable virus in about 40% of affected individuals, although new drugs (4, 5) that are likely to be approved this summer may almost double the rate of response in the difficult-to-treat genotype 1 infections. Progression to cirrhosis seems to be prevented in most patients who successfully clear the virus (6).

A major barrier to recognition of chronic HCV infection is the current testing strategy used in most laboratories. In contrast to hepatitis B virus, testing for which detects a viral protein (hepatitis B surface antigen) that confirms presence of the virus in the liver, HCV testing primarily relies on the detection of antibodies to HCV proteins. This approach has several limitations.

HCV antibody tests were developed to provide maximum sensitivity, because they were initially intended for use in screening blood donors. As with any test, maximizing sensitivity generally carries a risk of reduced specificity. In all anti-HCV tests (as is common for many infectious-disease tests), the manufacturers define a positive result as one with a signal greater than or equal to that of the arbitrary cutoff

value defined for that lot, which is usually expressed as a signal-to-cutoff (S/CO) ratio. Among samples with positive anti-HCV results but with a S/CO ratio only slightly  $>1.0$ , the percentage of false-positive results is high. Current guidelines from the CDC (7) recommend the use of a confirmatory test, typically a recombinant immunoblot assay (RIBA), for all samples with weakly positive results. The CDC has also determined thresholds for S/CO ratios above which at least 95% of results with each current assay would be true positives (available at <http://www.cdc.gov/hepatitis/HCV/LabTesting.htm>; accessed March 29, 2011).

The IOM report indicated that HCV diagnoses are often incomplete, because physicians have results only for anti-HCV tests (1). Outside of blood donor testing, few laboratories actually use RIBA to confirm weakly positive results, and individuals are often falsely identified as HCV exposed, which can produce patient anxiety and lead in some cases to difficulties in getting insurance and to unnecessary healthcare expenses in following up false-positive results. The IOM report recommends that positive anti-HCV results be confirmed with a second test, ideally before the information is presented to the patient (1). The purpose is both to prevent such false-positive results and to establish whether infection is current or resolved.

The approach of simply performing anti-HCV tests cannot answer this latter question, even with confirmation by RIBA. Detection of HCV RNA is the principal method used currently to recognize patients who are chronically infected (8); however, many patients with anti-HCV test results have never undergone testing for HCV RNA. This problem is an important one because, as one study showed, 31% of family physicians did not know what to do next when a positive anti-HCV result was reported for one of their patients (9).

In this issue of the Journal, Lai et al. (10) describe their evaluation of a reflex-testing approach to providing the answers recommended in the IOM report. They evaluated data from  $>3000$  patients with positive anti-HCV results who were identified prospectively. HCV RNA testing was performed reflexively in almost 80% of these anti-HCV–positive patients, with results becoming available within 30 days.

As also observed in prior investigations, Lai et al. found that most weakly positive results were negative by RIBA testing. They did not find any positive RIBA or

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<sup>3</sup> Nonstandard abbreviations: HCV, hepatitis C virus; IOM, Institute of Medicine; S/CO, signal-to-cutoff (ratio); RIBA, recombinant immunoblot assay.

HCV RNA results when the S/CO ratio was  $<3.0$ . Other investigators have also found a positive RIBA result to be quite rare in individuals with very low S/CO ratios, although the cutoff for terming a result “very low” varies by assay and by lot (11). The only extensive data available in this regard are for the assay used by the authors of this study. It seems reasonable not to perform RIBA testing for samples with low positive S/CO ratios, and such an approach would eliminate one of the major costs of performing reflex testing. In our institution, for example, 75% of weakly positive results had S/CO ratios  $<4.0$  (12).

Another important finding, which has also been reported by other investigators, is that a very high S/CO ratio detects almost all HCV RNA–positive samples. In their study, Lai et al. found that 95% of positive HCV RNA results were for samples that had an S/CO ratio  $>20.0$ . In contrast, RIBA results were almost always negative, even for individuals with negative HCV RNA results and a high S/CO ratio. Most of the patients with an S/CO ratio between 3.0 and 20.0 were negative for HCV RNA, with many of these individuals also negative in RIBA testing. Lai et al. thus suggested a possible cost-effective approach to performing reflex testing: no confirmatory testing if the S/CO ratio is  $<3.0$ , RIBA testing first if the S/CO ratio is between 3.0 and 20 (with RNA testing not needed if the RIBA value is negative or indeterminate), and RNA testing as the only confirmatory test if the S/CO ratio is  $>20.0$ .

Why should laboratories consider reflex-testing approaches in their own institutions? Because both the CDC and the IOM recommend confirmatory testing for appropriate patient care, some additional confirmatory procedure should be ordered to clarify the patient’s true HCV status. Most laboratories do not actually report the S/CO ratio to physicians, and no clinical guidelines actually discuss the S/CO ratio for interpreting anti-HCV results. Therefore, a physician is likely to interpret all anti-HCV results as true positives and to perform HCV RNA testing as a confirmatory test; however, physicians are not likely to consider RIBA as a confirmatory test. In my clinical experience, physicians confronted with a negative HCV RNA result often repeat the test several times before accepting that the patient is truly RNA negative. This repeated testing leads to unneeded healthcare expenses and, if the result is a false positive, unneeded emotional stress for the patients and their family. Reflex testing can be done in a very cost-effective manner (13) and be billed if such reflex panels are approved by the medical staff of the institution. With the likely increased emphasis on screening for HCV following the IOM report, laboratories can use the data of Lai and colleagues to develop

cost-effective strategies for reflex testing that provide appropriate data for physicians to correctly classify a patient’s true HCV status.

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