Recent advances in diagnosis and treatment are providing physicians with new options for managing patients with chronic HCV infection. The potential of these new technologies, however, can only be fully realized in the US if surveillance of new cases is improved; this can be achieved by establishing and implementing comprehensive test reporting requirements and by ensuring that physicians have a good understanding of appropriate test ordering and interpretation. Harmonized reporting standards, combined with physician education, will lead to improved identification of infected individuals and increased timeliness of medical interventions.

HCV presents a serious public health concern, infecting 170 million people worldwide [1] and >3.2 million people in the US, where it is the most widespread chronic blood-borne pathogen [2]. Additionally, HCV is the leading cause of chronic liver disease in the US [3] and the leading cause of death from liver disease, accounting for 8,000–10,000 deaths annually [4].

Recent advances in diagnosis and treatment are providing physicians with new options for managing patients with chronic hepatitis C. The potential of these new technologies will only be fully realized in the US if surveillance of new cases is improved; this can be achieved by establishing and implementing comprehensive test reporting requirements and by ensuring that physicians have a good understanding of appropriate test ordering and interpretation. Harmonized reporting standards, combined with physician education, will lead to improved identification of infected individuals and increased timeliness of medical interventions.

Improving surveillance of hepatitis C cases

An important public health goal in managing HCV infection is to improve the surveillance of new cases. Data currently available do not accurately reflect the prevalence of the disease and are an inadequate foundation for effective disease management and resource allocation [5]. Most individuals with chronic hepatitis C go undiagnosed and untreated for many years, at which point there is an increased risk for the development or progression of liver disease or liver cancer. Data from improved surveillance could provide a basis for enhanced health care, both in terms of access to care and appropriate level of care, but is dependent on two factors. First, public health departments need to receive complete, easily interpretable test results. Second, there needs to be timely identification of new cases to enable effective interventions.

With regard to reporting, laboratories in the US send test results to state public health departments, which in turn transmit data to the Centers for Disease Control and Prevention (CDC) via the National Notifiable Diseases Surveillance System (NNDSS). The data collected typically include diagnosis, event dates and basic demographic data (for example, state, county, age, race and ethnicity). Additional information collected by the Viral Hepatitis Surveillance Program (VHSP) includes clinical features, serological test results and risk factors for infection. There is, however, no national, standardized approach for laboratory test reporting – the CDC does not stipulate which data to collect; therefore, each state has established its own requirements resulting in a lack of consistency. For example, demographic data collected may vary from state to state, and only certain states require the reporting of alanine aminotransferase (ALT) test results. If the CDC is to harmonize reporting, it should establish recommendations for states to follow. The states in turn would then need to request laboratories operating in their state to collect the recommended information.
The scope of data included in any universal requirement will impact the timely identification of new cases. CDC guidelines issued in 2003 recommended that HCV testing include an option for reflex supplemental testing in addition to antibody testing (serology) to verify an anti-HCV-positive test result [6]. These guidelines sought to address the widespread practice of laboratories reporting a positive result based on a positive serology test result alone, and not verifying these results with more specific serological or nucleic acid testing (NAT). Supplemental testing was recognized as necessary to address the challenges of identifying chronic and acute HCV.

After acute exposure, HCV RNA is usually detected in serum before antibody; the presence of HCV RNA is generally detected within 1 week of infection [7], whereas anti-HCV may not be detectable before 8–12 weeks [8]. Analysing these two markers in combination allows for more accurate detection and reporting than that based solely on the presence of anti-HCV. A positive anti-HCV result alone would not distinguish between a resolved infection versus an acute HCV infection during a period of low-level viraemia or a false-positive assay result. A negative anti-HCV result alone would not identify early acute or chronic HCV infection in the setting of an immunosuppressed state [8].

Despite the 2003 guidelines, many sites today only conduct the serology test (Figure 1) and do not routinely test for HCV RNA [5]. This approach does not provide a definitive indication whether an individual is infectious or has a resolved infection.

The Institute of Medicine [5] and the American Association for the Study of Liver Diseases [8] have both recommended the inclusion of routine testing for HCV viraemia. This would enable identification of those at risk of transmission who may not be identified by serology testing alone, that is, individuals recently infected who are seronegative but are HCV-infected. NAT allows such acute cases of infection to be identified prior to the development of antibodies, enabling public health departments to take effective action. Conversely, if an individual is antibody-positive but has no viral RNA detected they are at reduced risk for transmission because the infection has been functionally eradicated and they may be less infectious than if they had demonstrable viraemia. From a surveillance point of view, these people do not necessarily need to go into care but they can still be viewed as being at risk of reinfection and should be informed.

Although it may be beneficial for laboratory companies to start reporting more comprehensive information, they are unable to do so unless physicians order the appropriate tests. Such a change will only occur with physician involvement and education on appropriate test ordering. This will increase understanding that a patient who is antibody-positive could be either HCV-RNA-positive or
HCV testing and reporting practices

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A test for viraemia should be ordered in addition to a serology test to determine infection definitively. Although qualitative tests are available for this purpose, quantitative tests are sufficiently sensitive and may serve as a diagnostic test for infectivity, while also providing the clinician a baseline viral load (Table 1). Physician education should raise awareness that a quantitative viral load test is required to monitor patients on therapy, while offering a streamlined, cost-effective approach to testing.

Finally, there is a case to be made for including ALTs in harmonized test reporting. Elevated ALT can be used to confirm that aspartate aminotransferase (AST) elevations are of liver origin, since elevation of both AST and ALT strongly suggest hepatocellular injury. This would indicate a need for further testing, including hepatitis A, B and C. If the patient was already immunized against HBV and HAV, it would be important to rule out HCV infection. If the patient history has documentation of both immunization and antibody response to HAV and HBV it may be unnecessary to test for these two viruses and more cost-effective to test for HCV only.

Table 1. HCV RNA tests available from Quest Diagnostics

<table>
<thead>
<tr>
<th>Test name</th>
<th>Sensitivity/Range</th>
<th>Description</th>
<th>Utilization</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Qualitative</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCV RNA qualitative, TMA</td>
<td>7.5 IU/ml</td>
<td>RNA is extracted from the patient sample and amplified by utilizing two enzymes (reverse transcriptase and T7 RNA polymerase) to cycle between RNA and DNA intermediates, resulting in several billion RNA amplicons.</td>
<td>Detect acute infection prior to seroconversion (that is, within 1–2 weeks post-exposure).</td>
</tr>
<tr>
<td>HCV RNA qualitative, PCR</td>
<td>50 IU/ml</td>
<td>Viral RNA is reverse-transcribed to cDNA and amplified with biotin-labelled HCV-specific primers. Amplification products are then hybridized to HCV-specific capture probes and detected with an avidin–HRP conjugate in a colourimetric assay.</td>
<td>Differentiate between resolved and active infection. Demonstrates resolution of infection.</td>
</tr>
<tr>
<td><strong>Quantitative</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCV RNA quantitative, real-time PCR</td>
<td>43–69,000,000 IU/ml</td>
<td>Real-time PCR.</td>
<td>Confirm active HCV infection.</td>
</tr>
<tr>
<td>HEPTIMAX®</td>
<td>5–69,000,000 IU/ml</td>
<td>Real-time PCR, followed by quantitative TMA.</td>
<td>Document rapid virological response.</td>
</tr>
<tr>
<td>HCV RNA quantitative, PCR</td>
<td>0.7–7.500 IU/ml</td>
<td>Quantitative TMA.</td>
<td>Guide duration of therapy.</td>
</tr>
<tr>
<td></td>
<td>0.70–3.88 IU/ml</td>
<td></td>
<td>Confirm resolution of infection (sustained virological response).</td>
</tr>
<tr>
<td><strong>Genotype</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCV RNA genotype, LiPA</td>
<td>&gt;300 IU/ml</td>
<td>Reverse transcription and PCR amplification of specific regions of HCV genome. LiPA utilizing genotype-specific probes from the HCV core region and 7 regions of the 5′-UTR. Distinguishes among major types and most common subtypes of HCV: 1, 1a, 1b, 1a/b; 2, 2a/c, 2b; 3, 3a, 3b, 3c, 3k; 4, 4a/c/d, 4b, 4c, 4f, 4h; 5, 5a; and 6, 6a/b, 6c-1.</td>
<td>Determine whether to begin antiviral therapy in patients with chronic HCV infection. Assess need for liver biopsy. Determine duration and dosage of treatment. Predict response to therapy.</td>
</tr>
<tr>
<td><strong>Quantitative rt to genotype</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HEPTIMAX® rt to genotype, LiPA</td>
<td>5–69,000,000 IU/ml</td>
<td>Line-probe hybridization assay to identify genotype and subtype.</td>
<td>Predict likelihood of therapeutic response.</td>
</tr>
<tr>
<td>HCV RNA quantitative, real-time PCR rt to genotype</td>
<td>43–69,000,000 IU/ml</td>
<td>DNA sequencing to identify genotype and subtype.</td>
<td>Determine the duration of treatment.</td>
</tr>
</tbody>
</table>

*Quest Diagnostics Inc., San Juan Capistrano, CA, USA. †This test is no longer available from Quest Diagnostics. ‡Roche Molecular Systems, Inc., Branchburg, NJ, USA; limit of detection (LOD) 7.1 IU/ml for genotype 1. cDNA, complementary DNA; EIA, enzyme immunoassay; HRP, horseradish peroxidase; LiPA, line-probe assay; TMA, transcription-mediated amplification; VL, viral load.
Requirements for harmonized reporting should include a combination of anti-HCV and NAT testing, together with AST and ALT. Such an approach is recommended in the CDC’s guidelines for viral hepatitis surveillance and case management [9]. These include a draft viral hepatitis case report, which could serve as a model for state reporting.

The impact of new therapies on testing and patient management

HCV protease inhibitors are now available for treating chronic hepatitis C. The advent of these new therapeutic agents, also called direct-acting agents (DAAs), is impacting HCV RNA testing in two ways: requirements for monitoring frequencies and for sensitivity of detection (Table 2).

Since these new therapies enable a strictly ‘programmed’ regimen – identify genotype, initiate treatment, monitor at set interval – it is possible that adoption of the regimen will lead to a broader spectrum of physicians treating the disease. One can foresee that patients with normal or minimally elevated ALT levels will not require referral. Care for these patients could move from hepatologists and infectious disease physicians to internists and family physicians, while those individuals with more severe liver damage, that is, cirrhotics, would be cared for by hepatologists. Such a change will only occur following comprehensive physician education over an extended period of time. The experience of HIV-infected patient management, where care shifted from specialists to generalists following the widespread availability of antiretrovirals, suggests that for hepatitis C the same approach is a possibility, and one made all the more likely by the fact that hepatitis C treatment has a defined end point (eradication of infection).

Testing implications of new drug classes

With new therapies emerging, there are going to be considerably more options for clinicians to effectively eradicate HCV infection. As with any new class of drug, there will be an evolutionary process in understanding how to treat patients effectively, and how best to use these drugs and in what combination (whether or not they will include interferon and ribavirin). Any new regimen established is likely to include the same monitoring approach as that for most recently approved DAAs. Studies published on the new therapies have been based on the same parameters for monitoring and defining success as have been established for currently licensed drugs. Response-guided therapy eligibility for previously untreated patients is determined by an ‘undetectable’ NAT result at weeks 4 and 12 for boceprevir and at weeks 8 and 24 for telaprevir. There is no indication that level of sensitivity for NAT will change for drugs in development.

One area of uncertainty in relation to HCV drug development is that of resistance testing. As development of new therapies continues, a considerable amount of clinical information is being gathered to help understand how, when or if resistance testing fits into clinical management of hepatitis C [10–15]. Although resistance is demonstrable, the question remains whether resistance testing for HCV is clinically relevant. Experience with HIV and HBV would indicate this is likely; however, in the context of triple therapy and the minority nature of variants that demonstrate resistance, resistance testing may be considered less relevant than the clinical response to drug therapy.

Conclusions

Technological advances in HCV testing and therapies are sources of optimism for more effective management and treatment of HCV patients. Diagnostic technologies, such as quantitative NAT, enable clinicians to identify infection and monitor therapy more effectively, while offering the potential for a more streamlined, cost-effective approach to testing. To capitalize on the potential of these technologies, state public health departments could standardize reporting requirements to enhance surveillance of new cases. These should be based on the minimum data needed to identify infected individuals and enable timely interventions and be supported by physician education on the appropriate ordering and interpretation of tests.

Disclosure statement

The author declares no competing interests.

References


