Review

Testing for HCV: the first step in preventing disease transmission and improving health outcomes for HCV-infected individuals

John W Ward*

1Centers for Disease Control and Prevention, Division of Viral Hepatitis, Atlanta, GA, USA

*Corresponding author e-mail: jww4@cdc.gov

In the US, application of antibody-based and nucleic acid testing for HCV has dramatically reduced HCV transmissions over the past two decades. In addition to testing donors of blood, tissue and organs to reduce the risk of transfusion/transplantation-associated HCV, testing can also motivate individuals to adopt safer behaviours. HCV testing, when accompanied by appropriate care and treatment, can reduce the extent of morbidity and mortality that often accompanies chronic HCV infection. Options for HCV treatment have recently been expanded and improved with the availability of more effective, anti-HCV drugs; furthermore, the remarkable results of clinical trials of these drugs suggest that safe, all-oral therapies requiring relatively short duration are on the immediate horizon. These advances have prompted new US initiatives to recommend HCV testing to the wider community (including those populations with a high prevalence of hepatitis C) and promote linkage to treatment for those found to be HCV-infected. Crucial to the success of these initiatives are the development of tests capable of identifying active infection, recent infection, or both, and the implementation of testing strategies that facilitate broad access to HCV testing linked to care and treatment.

Introduction

Laboratory testing for HCV has been the cornerstone of patient- and population-based hepatitis C prevention worldwide since the development of serological assays in 1990. In the absence of a hepatitis C vaccine, only through knowledge of HCV infection status can infected patients be identified and receive care and treatment to reduce the likelihood of disease and of transmitting their infection to others. Additionally, data obtained through serological HCV testing are instrumental in informing prevention at the population level.

Results of HCV tests are necessary to confirm the epidemiology of HCV transmission, helping to describe the populations at highest risk for infection (for example, injection drug users [IDUs], dialysis patients and other individuals with blood-borne exposures), as well as other exposures associated with HCV transmission (for example, perinatal, health-care and sexual exposures) [1]. HCV testing has also enabled better characterization of the natural history of HCV infection. Data from serological testing have shown that approximately 80% of individuals who acquire HCV become chronically infected; these data were used to inform further studies that revealed the adverse consequences of chronic HCV infection, including cirrhosis and hepatocellular carcinoma (HCC). After 25–30 years of infection, 15–35% of HCV-infected individuals will develop cirrhosis [2], 1–4% of whom will progress to liver cancer each year [3].

Implementation of testing policies can directly affect HCV transmission on a large scale. For >20 years, the World Health Organization has recommended that all donated blood and blood products be screened for HCV [4], leading to dramatic reductions in HCV transmission among individuals receiving these products. In the US, donated blood has been screened for HCV since 1992 [5]; shortly thereafter, screening was extended to include tissue and organ donors [6]. HCV screening, which must include both anti-HCV and nucleic acid tests (NATs), has successfully been employed to virtually eliminate transfusion-associated HCV infection. However, such testing remains a challenge in resource-constrained settings.
Testing for HCV in the US

Antibody tests are typically the first-line of HCV testing when determining whether an individual has been exposed to HCV. For individuals with positive anti-HCV test results, this testing should be followed by supplemental tests, typically an immunoblot assay to confirm the presence of HCV antibody. However, these supplemental tests can be costly, requiring use of specific equipment and expertise. Consequently, such testing is often not performed by laboratories. As a substitute, many laboratories in the US use the strength of the measure of HCV antibody on the first test (known as the signal-to-cutoff ratio) as an indirect measure to identify a true positive for HCV antibody. Each laboratory test has a different signal-to-cutoff value and requires evaluation to identify the one most indicative of a true positive test for HCV antibody.

Serological testing to determine active, chronic HCV infection is met with the same challenges in equipment and expertise, limiting access to these virological assays. As a result, among the limited number of HCV-infected individuals who receive an initial HCV test followed by confirmatory antibody testing, even fewer are aware of their virological status. Moreover, except in the relatively rare instances of identifying virus in the absence of antibody, newly acquired cases of HCV infection cannot be distinguished from past infection using available HCV tests. An assay for newly acquired HCV infection would help public health officials identify emerging modes of transmission (as well as new populations potentially at risk) and help clinicians offer HCV therapy in the acute stage of infection when HCV therapy is most effective in clearing virus from the body.

Need for new US testing strategies

These limitations in HCV testing pose formidable challenges for prevention of HCV infection at a time of increasing HCV-associated morbidity and mortality in the US. HCV infection greatly raises risk for liver disease, including HCC. In contrast to most other forms of cancer, rates of HCC are on the rise, increasing 2.5% each year during 1999–2008 [7]; at least 50% of this increase is attributable to HCV [8]. HCV-associated disease is the leading indication for liver transplantation [9–12]. In a retrospective analysis of 1985–2006 registry data obtained from all US liver transplant centres, 40,293 (36%) of 113,927 individuals on the liver transplant waiting list were infected with HCV [13]. High rates of HCV-related morbidity are expected to continue for several decades; without therapy, 1.76 million Americans (61%) will develop cirrhosis and 418,000 (14%) will develop liver cancer [14]. The adverse health consequences of hepatitis C are contributing to rising rates of HCV-associated death. Between 1999 and 2007, recorded deaths from hepatitis C increased significantly from 7,555 to 15,106 [15], representing a 50% increase in mortality. A model used to forecast future HCV-related mortality based on hepatitis C prevalence estimates that of approximately 2.9 million Americans that were living with chronic HCV infection in 2005, approximately 1.1 million (37%) are expected to die from hepatitis C by 2060 in the absence of treatment [14].

In the US, HCV testing is directed to individuals with recognized risks for HCV transmission. Because of their risk behaviours, IDUs are at increased risk for HCV infection [16,17]; comorbidities (for example, HIV infection) also affect IDUs, many of whom have inadequate access to and receipt of health services. Although this population can be hard to reach, studies have shown that when provided, prevention services have contributed to a decline in overall prevalence of HCV infection in some cohorts of IDUs. High rates of HCV infection persist in other IDU cohorts [18], including new injectors [19,20]; individuals who are incarcerated, many of whom have a history of injection-drug use, also continue to have a high burden of HCV infection [21]. Health-care-associated transmission of HCV related to unsafe injections and poor infection control is a cause of outbreaks in the US and remains the leading cause of HCV transmission in many countries. HCV is also spread perinatally and through sexual contact; sexual transmission, which is increasingly contributing to HCV transmission among HIV-positive men who have sex with men in Europe, has recently been documented in New York City [22,23]. Data from serological surveys and HCV surveillance can help inform HCV prevention and control policies by revealing the unique needs and characteristics of risk populations that would most benefit from targeted prevention services.

A risk-based approach to testing is not the only strategy for identifying HCV-infected individuals. In the US, such an approach has met with limited success, failing to identify up to 75% of individuals living with HCV [24]. Alternatively, HCV testing strategies can focus on populations with a high burden of disease. HCV-related morbidity and mortality resulting from chronic HCV infection disproportionately affect individuals born between 1945 and 1965 (the so-called ‘baby boom’ generation), most of whom have been infected for several decades and are at increasing risk for HCV-associated cirrhosis and HCC as they age. This large population of Americans currently accounts for 75% of all HCV-infected adults in the US and 75% of all HCV-related mortality. African Americans also shoulder a disproportionate burden of HCV infection, being twice as likely to be infected with HCV as the general population [25]. Although recent advances have been made in...
preventing and treating HCV, many HCV-infected persons, including those aware of their infection status, do not receive appropriate care and treatment.

Knowledge of infection status, followed by linkage to care and treatment as appropriate is particularly important with the availability of more effective anti-HCV therapies, including telaprevir and boceprevir. Compared with pegylated interferon/ribavirin therapy alone, the addition of telaprevir or boceprevir to the treatment regimen has increased the potential for viral clearance from 38% to 63% and 46% to 79%, respectively [26,27], improving health outcomes for individuals living with HCV infection and preventing ongoing disease transmission. HCV therapies are expected to continue to improve. Therapies currently under study in clinical trials hold great promise for the advent of interferon-free, oral regimens that are highly effective, safe and require shorter duration of therapy [28]. As these new treatments become available they can be integrated into HCV testing programmes to cure hepatitis C among individuals with ongoing risk behaviours and eliminate risk for HCV transmission. In an era of highly effective therapies, the elimination of HCV through effective strategies for testing and treatment is an achievable goal for the US and perhaps for other countries experiencing high rates of chronic infection and ongoing HCV transmission.

New US initiatives for HCV testing and treatment

To ensure that more individuals are tested and linked to care and treatment, new policies have been developed and existing initiatives revised. In 2011, the US Department of Health and Human Services published a viral hepatitis action plan, which provides a roadmap for guiding the nation’s public health response to viral hepatitis by presenting explicit steps for improving prevention and enhancing the care and treatment provided to infected individuals [21].

The action plan highlights the need to expand access to testing in health settings serving populations experiencing viral-hepatitis-related disparities. Also called for is development and implementation of new testing technologies, such as point-of-care (POC) tests for HCV; these newly available rapid tests can facilitate testing, notification of results and post-test counselling, and referral to care at the time of the testing visit [29]. POC HCV tests also can be used simultaneously with HIV rapid testing for individuals at risk for both HCV and HIV infections. Beginning in 2012, the Centers for Disease Control and Prevention (CDC) will increase public health capacity for HCV screening by supporting local efforts to enhance testing among individuals for whom it is indicated and ensure that individuals living with chronic hepatitis C are informed, appropriately counselled and linked to care. To promote delivery of these prevention services to individuals with the greatest need, funding will be directed to HCV testing activities in diverse settings (for example, health departments, community health centres and substance abuse treatment facilities) serving high-risk populations.

Because individuals born between 1945 and 1965 account for a substantial percentage of chronic hepatitis C cases in the US, the CDC has expanded its current risk-based HCV screening guidelines to include a birth cohort approach to testing [30]. When fully implemented, such an approach could avert 80,000–120,000 HCV-associated deaths [31]. Identifying individuals in this birth cohort is a cost-effective [31] first step to ensuring that individuals living with hepatitis C receive care and treatment that can improve health and prevent transmission.

Future needs

In this era of increasingly effective therapy, the role of HCV testing is paramount in disease surveillance, enabling the provision of care and treatment to HCV-infected individuals and facilitating the monitoring of response to therapy. Changes in viral hepatitis policy – guided by a country’s HCV epidemiology, social/cultural context for prevention and health-care system capacity – can help expand the number of individuals who are tested for HCV and receive care and treatment. Like the US, other countries might benefit from implementing national plans for viral hepatitis prevention, care and treatment. However, to maximize the effect of these policies on disease transmission and HCV-associated morbidity and mortality, additional improvements in viral hepatitis diagnostics are needed. Governmental agencies can collaborate with academic and industry partners to develop and implement POC tests and assays capable of distinguishing between acute and chronic hepatitis C. The advent of less costly alternatives to current HCV NATs can help ensure access to confirmatory HCV testing; in the US, fewer than one fourth of public health laboratories conduct PCR testing to confirm positive anti-HCV serological test results.

To reduce the minimal but continued risk of HCV infection among recipients of donated organs, additional changes in federal policy are needed. Although NAT can more accurately and promptly detect HCV than anti-HCV testing alone, US organ procurement organizations (and perhaps those in other countries) are not required to screen donors using the NAT platform. Eliminating risk for HCV transmission to organ recipients is not foreseeable because of assay-related issues and laboratory error [32]; however, requiring procurement organizations to conduct NAT would bring the risk closer to zero.
Additional obstacles must be overcome to enhance HCV testing in the US. As identified in the viral hepatitis action plan, the low level of HCV-related knowledge and awareness by providers and the patients they serve contributes to suboptimal testing rates; providers often fail to ask patients about HCV-associated risk behaviours and miss opportunities to test patients with known risk factors. Regardless of the development of new tests and therapies, successful HCV prevention initiatives hinge on a well-informed health-care workforce capable of using these tools to prevent infection and improve health outcomes for those living with hepatitis C. A final barrier to testing is associated with access to care; individuals at highest risk for hepatitis C may not benefit from the latest advances in diagnostics and treatment because they often lack health insurance and regular sources of health care.

Conclusions

For individuals living with hepatitis C, HCV testing is the gateway to care and new HCV therapies capable of dramatically reducing morbidity and mortality. Efforts are needed to improve HCV diagnostics, particularly through development of POC tests and assays capable of distinguishing between acute and chronic infection. Equally important is the development of public health policies linking HCV-infected individuals to care and treatment. Through strategic planning, capacity building, and partnerships, barriers to HCV testing can be overcome, leading to more individuals being aware of their HCV infection and new opportunities to reduce and eventually eliminate HCV-associated transmission and disease.

Disclosure statement

The author declares no competing interests.

References


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