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eViralHepatitis Review
VOLUME 3, ISSUE 9

HCV SCREENING AND NATURAL HISTORY

In this Issue...

Hepatitis C infection is a major public health challenge: it is the most common chronic blood-borne pathogen in the United States and the leading indication for liver transplantation. However, HCV-related morbidity and mortality are preventable with early screening and appropriate counseling and treatment for patients with high risk.

In this issue, we review recent literature describing:

- The findings that informed the USPTS and CDC recommendations for birth cohort screening recommendations
- HIV, age, and severity of HCV-related liver damage
- The prevalence of hepatitis infections (HCV and HBV) in clinical practice

LEARNING OBJECTIVES

After participating in this activity, the participant will demonstrate the ability to:

- Identify patients for whom HCV treatment is urgent.
- Define patients with HCV who need referral.
- Recognize patients who require HCV testing.

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STATEMENT OF NEED

HCV
- Clinicians do not adequately identify which of their patients are at highest risk for HCV infection or effectively interpret testing results.
- Clinicians need to understand best practices in how to identify and manage HCV treatment-related side effects.
- Clinicians need improved awareness of how newly emerging therapies impact therapeutic decision-making in HCV infected and HIV/HCV co-infected patients.
- Clinicians are unaware of new non-invasive techniques to stage liver disease.
- Clinicians need to understand best practices in identifying cirrhosis and HCC in patients infected with HCV.

HBV
- Clinicians do not effectively identify their patients at risk for HBV.
- Clinicians are unaware of new non-invasive techniques to stage liver disease.

Program Information

CME Info
Accreditation
Credit Designations
Intended Audience
Learning Objectives
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Length of Activity

1.0 hour Physicians
1.0 contact hour Nurses

Launch Date

April 29, 2014

Expiration Date

April 28, 2016

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- Clinicians need to understand best practices in identifying cirrhosis and HCC in patients infected with HBV.

INTENDED AUDIENCE

The target audience (clinicians) for this initiative includes: OB/GYNs, NPs, PAs, hepatologists, gastroenterologists, infectious disease physicians, community gastroenterologists and others who care for patients of Asian and West African descent in areas of high HBV prevalence.

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- **Raymond T. Chung, MD,** discloses that he has served as a consultant for AbbVie, Inc. and Idenix and has received grant/research funding from Gilead and Mass Biologics.

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IN THIS ISSUE

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David Thomas, MD has disclosed that he has received grants from Gilead Sciences, Inc. and Merck.

Unlabeled/Unapproved Uses

Dr. Thomas has indicated that there will be no references to unlabeled/unapproved uses of drugs or products.

Program Directors' Disclosures

COMMENTARY

In 2007, HCV-related mortality surpassed that caused by HIV, and HCV accounts for half of the recently observed threefold increased incidence of hepatocellular carcinoma.[1] As the population of people infected with HCV ages, HCV-related morbidity and mortality are expected to double in the next decade.[2] The significance of aging in the incidence of HCV-related morbidity is underscored in the paper by Kirk and coworkers reviewed in this newsletter. The authors had previously published low estimates of disease burden in this large cohort of drug users. However, now that the cohort is 10 years older, there is a marked increase in cirrhosis. Within the cohort, persons with cirrhosis were more than twice as likely to be in the upper age quartile.

Fortunately, HCV-related morbidity and mortality are preventable. An inexpensive, highly sensitive screening test is available to detect HCV infection, and an accurate, minimally-invasive blood test can confirm positive screening test results. The review of the May 10, 2013 MMWR from the Centers for Disease Control and Prevention (CDC) discusses how the recommended approach to HCV testing has been updated to reflect two important changes: the availability of a point-of-care test and the lack of supplemental antibody testing. The waiver given for use of point-of-care testing may make it possible to test for HCV in settings like STD clinics and to give post-test counseling before the patient leaves. That is a major step forward for public health campaigns to control HCV infection. The new algorithm for testing is much easier to follow than previous testing schemes and, by simplifying the process, should help expand HCV testing.

HCV infection can be cured, and cure rates have risen sharply in recent years.[3,4] Cure of HCV infection reduces the risk of cirrhosis, liver failure, hepatocellular carcinoma, and death.5,6 Although since 1998 there have been guidelines calling for screening persons for HCV risk factors and testing those with risk, fewer than 50% of people infected with HCV are aware of their status. That point is emphasized in the article by Spralding and coworkers. Looking at a large managed care health plan (which should be representative of many Americans), they found that 12.7% of all patients were tested, and nearly half (5.5%) were positive. More important was what they didn't find. Drawing on general population data, the investigators project that at least as many people with HCV were missed by this strategy. Presumably, those HCV infections would continue to progress silently and the patients would not benefit from treatment. Lack of awareness of HCV infection will markedly diminish the impact of treatment nationwide.

The CDC has evaluated alternative strategies for detecting HCV infection. In a series of studies based on the National Health and Nutrition Examination Study data, it was evident that an estimated 60%-75% of those infected with HCV in the United States were born between 1945 and 1965, and that cohort has an HCV prevalence (4%), more than five-fold higher than in people born in other years.[7] The CDC's analysis suggests that testing those born in this 1945-1965 birth cohort would be cost-effective, would identify for the first time more than 800,000 persons with HCV infection, and would save approximately 121,000 lives.[7] Thus, the paper by Smith and coworkers builds on that work and formulates new national screening strategies. These culminated on August 17, 2012 with the CDC recommendation that everyone born between 1945 and 1965 be tested for HCV infection.

In a separate process, the US Preventive Services Task Force (USPSTF) reviewed the evidence for HCV screening and treatment and concluded that there was a clear benefit to successful HCV treatment. As described in the paper by Chou and coworkers, the USPSTF also considered evidence for and against testing for HCV. In an initial draft document, USPSTF endorsed risk-based testing with a highly regarded "B" grade, but gave the birth cohort recommendation a provisional "C" grade. Fortunately, that decision was recently reversed and now both CDC and USPSTF recommend both risk-based and birth-cohort testing for HCV infection.

Both risk-based screening and birth-cohort screening are justifiable and complementary.

However, the birth-cohort approach is more amenable to performance measurements than the risk-based approach. In a recent review of medical records representing 1,279,207 outpatient visits for 208,752 patients, only 2.6% of patient records contained risk information. Thus, both strategies should be employed to increase HCV detection and

ensure that all individuals have the opportunity to benefit from forthcoming breakthroughs in HCV treatment. (Spradling)

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SYSTEMATIC REVIEW OF HEPATITIS C SCREENING STRATEGIES

Chou R, Cottrell EB, Wasson N, Rahman B, Guise JM. Screening for hepatitis C virus infection in adults: a systematic review for the U.S. Preventive Services Task Force. *Ann Intern Med*. 2013 Jan 15;158(2):101-108

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In 2004, the United States Preventive Services Taskforce (USPSTF) did not find sufficient evidence to recommend HCV screening. In this study, to inform updated recommendations, Chou and coworkers reviewed the publications on HCV screening from 1947 to May 2012, focusing on screening strategies and their ability to identify persons infected with HCV and any unanticipated harms. This article did not consider the tests used to detect infection.

The investigators sought to answer four general questions:

Q1: Does screening for HCV infection in nonpregnant adults without known abnormal liver enzymes reduce mortality and morbidity from HCV infection, affect quality of life, or reduce HCV incidence?

The answer was that there was insufficient evidence because studies were not designed to compare groups in which screening was either done or omitted.

Q2 & 3: What is the effectiveness on clinical outcomes of different risk- or prevalence-based methods for screening for HCV infection? What is the sensitivity and number needed to screen to identify one case of HCV infection using different risk- or prevalence-based methods for screening for HCV infection?

In high-prevalence settings, the investigators found evidence that risk-based screening could have high sensitivity. For example, one study of 1000 patients attending an inner-city primary care clinic with a prevalence of 8.3% found that a strategy of testing patients with

positive findings in at least one of three domains (medical history, exposure history, or social history) would have a sensitivity of 92% and a number needed to screen to find one infection of 9.3.1 However, 71% of the clinic would have still been tested.

With most studies, more narrowly targeted strategies could be identified by only testing very high-risk persons, such as those with a history of injection drug use, hence reducing the number tested to find one positive to < 2.[2] However, this gain was achieved at the cost of missing more than half of the infections.

Q4. What are the harms associated with HCV screening, including diagnostic liver biopsy?

Some studies recognized the psychological impact of testing, including stigmatization and spousal tensions. In addition, many studies documented risks associated with liver biopsy. The risks of liver biopsies have been estimated to be 1%-3% for hospitalization after a Tru-Cut needle biopsy.[3]

The authors concluded that prospective studies were needed to understand the effects of different screening strategies on the diagnostic yield and clinical outcomes.

It is noteworthy that the lack of population-based data to justify HCV screening (Q1) does not mean that the practice cannot be justified. Instead, the case for screening has to be made incrementally by demonstrating the benefits of successful treatment and logically that beneficial treatment is not possible for persons with unrecognized infections.

This investigation is important in that it focuses on identifying people with HCV infections. It is likely that the effectiveness of screening strategies will vary in different settings. Abundant evidence shows that the strategy of relying on clinicians to identify risk factors during a busy clinical practice and test those who are positive will not be effective. Strategies that either bring the risk identification out of the doctor-patient encounter and/or destigmatize risk identification are likely to be more effective. In that regard, it is notable that both the CDC and USPSTF endorse HCV testing of persons with risk factors and routine testing of persons in high-prevalence situations (such as those born between 1945 and 1965). The latter practice is expected to identify more than 75% of all people infected with HCV, irrespective of their "risk practices."

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BIRTH COHORT TESTING FOR HCV INFECTION

Smith BD, Morgan RL, Beckett GA, Falck-Ytter Y, Holtzman D, Ward JW. Hepatitis C virus testing of persons born during 1945-1965: recommendations from the Centers for Disease Control and Prevention. *Ann Intern Med*. 2012 Dec 4;157(11):817-822.

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Investigators from the US Centers for Disease Control and Prevention (CDC) and related agencies formulated recommendations for HCV testing to augment their 1998 recommendations. Evidence had accumulated from multiple studies that more than half of people with HCV infection in the US were unaware of their status, despite the presence since 1998of a risk-based testing guideline. Investigators reviewed the literature on HCV epidemiology in the US from 1995 to February 2012. Two new recommendations were formulated:

Recommendation 1. The CDC recommends that adults born during 1945-1965 should receive one-time testing for HCV without prior ascertainment of HCV risk.

This recommendation was largely justified by the results of the serial National Health and Nutrition Examination Surveys (NHANES). The studies that have examined the prevalence of HCV have consistently found that persons born between 1945 and 1965 have an HCV prevalence more than five times higher than adults born in other years. In the most recent NHANES report on HCV testing, the prevalences were 3.25% for the 1945-1965 group vs 0.80% for those born outside the birth cohort.

Also central to this recommendation were data demonstrating that successful HCV treatment reduces HCV-related and all-cause morbidity and mortality. The CDC investigators found evidence that persons who were successfully treated had a reduced incidence of liver failure and hepatocellular carcinoma and had improved quality of life.[1]

In a separate paper, CDC investigators modeled the effectiveness of this recommendation.[2] Compared to the status quo, birth cohort screening was projected to identify 808,580 additional cases of chronic HCV infection, at a cost of $2874 per case identified. If followed by currently approved HCV treatments, a one-time HCV test of persons born 1945-1965 was found to be cost-effective at $35,700 per quality-adjusted life year gained.

Recommendation 2: The CDC recommends that all persons identified with HCV infection should receive a brief alcohol screening and intervention as clinically indicated, followed by referral to appropriate care and treatment services for HCV infection and related conditions.

This recommendation was largely based on the well-established link between heavy alcohol use and more rapid progression of HCV infection. In addition, CDC investigators considered 22 randomized, controlled trials that demonstrated that "interventions" could reduce alcohol consumption by a mean of 38.42 grams each week.

This paper is important principally because it provides the basis for a novel strategy for identifying HCV infections in the US. There is widespread agreement that the old risk-based strategy was insufficient. The underlying assumptions and scientific basis for the birth cohort testing recommendation are sound. Whether this new recommendation is effective depends of course on the degree to which the strategy is implemented. Recent endorsement by the US Preventive Services Taskforce should help, as it will provide a basis for large managed care organizations and insurance companies to implement.

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1. Chou R, Hartung D, Rahman B, Wasson N, Cottrell EB, Fu R. Comparative effectiveness of antiviral treatment for hepatitis C virus infection in adults: a systematic review. *Ann Intern Med*. 2013;Jan 15;158(2):114-123.
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NEW HCV TESTING RECOMMENDATIONS

Centers for Disease Control and Prevention (CDC). Testing for HCV infection: an update of guidance for clinicians and laboratorians. *MMWR Morb Mortal Wkly Rep*. 2013 May 10;62(18):362-365.

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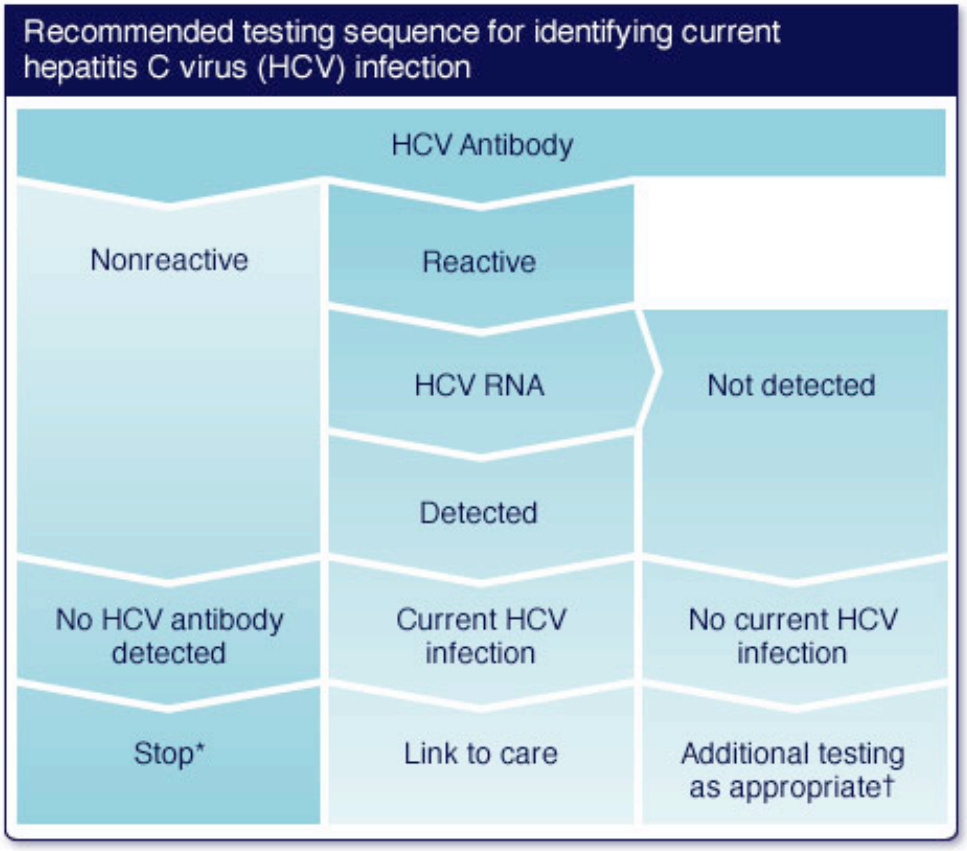
Two major changes in the assays for HCV testing led the US Centers for Disease Control and Prevention (CDC) to change the recommended strategy for testing. First, the Chiron RIBA HCV 3.0 Strip Immunoblot Assay (Novartis Vaccines and Diagnostics) that was recommended for supplemental testing of blood samples after initial HCV antibody testing is no longer available. Thus, the testing algorithm that included confirmation of HCV antibodies by RIBA had to be changed. Second, the US Food and Drug Administration

provided a waiver for OraQuick HCV Rapid Antibody Test (OraSure Technologies) to be used in nontraditional settings such as physician offices and other freestanding counseling and testing sites as a point of care HCV screening test.

The new HCV testing recommendation still begins with detection of HCV antibodies by enzyme immunoassay (see figure below). Now, initial detection of HCV antibodies can be made either by commercial laboratories testing serum or plasma collected by routine venipuncture or at the point of care with fingerstick-derived capillary blood. The sensitivity and specificity of the OraQuick assay was found to be similar to those of FDA–approved, laboratory-conducted HCV assays (see excellent review by Shivkumar et al, referenced below).1 In persons with a positive HCV screening antibody test, blood should be tested for HCV RNA. If both HCV antibodies and RNA are present, the person is infected with HCV. If the HCV RNA test is negative in a person with HCV antibodies, it is possible that individual is among the 20%-40% who spontaneously resolve HCV infection. Another possibility is that the screening test was false-positive. Previously, the RIBA test could differentiate the two with high confidence, but now it can be difficult to distinguish. Commercial labs often report a signal-to-cutoff ratio (s/co) of the screening EIA, and lower values are associated with false positive test results. In addition, testing for HCV antibodies with another FDA approved test can improve the specificity.

Despite the name, the OraQuick test is approved only for fingerstick- derived capillary blood and not salivary samples. The accuracy of salivary testing was lower.



* For persons who might have been exposed to HCV within the past 6 months, testing for HCV RNA or follow-up testing for HCV antibody is recommended. For persons who are immunocompromised, testing for HCV RNA can be considered.
†To differentiate past, resolved HCV infection from biologic false positivity for HCV antibody, testing with another HCV antibody assay can be considered. Repeat HCV RNA testing if the person tested is suspected to have had HCV exposure within the past 6 months or has clinical evidence of HCV disease, or if there is concern regarding the handling or storage of the test specimen.

Centers for Disease Control and Prevention. *Morbidity and Mortality Weekly Report (MMWR)*. May 10, 2013;62(18):362 ñ 365.

Reference

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HIV, AGE AND THE NATURAL HISTORY OF HCV

Kirk GD, Mehta SH, Astemborski J, et al. HIV, age, and the severity of hepatitis C virus-related liver disease: a cohort study. Ann Intern Med. 2013 May 7;158(9):658-666.

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This study considered the results of 5634 liver elastograpy results from 1176 former or current injection drug users with HCV antibodies. Elastography has emerged as a surrogate to liver biopsy for evaluating liver fibrosis stage in persons with HCV and other liver diseases. Because the test is very well tolerated, it is possible to use it in large clinical studies.

Among the 1176 patients who were anti-HCV positive, 34% were coinfected with HIV. The median age at the first elastography assessment was 49 years. Higher liver fibrosis scores were found in persons who were HIV coinfected and older ($P < 0.001$). For example, cirrhosis was found in 19.5% of those who were HIV/HCV coinfected compared to 11.0% of those without HIV ($P < 0.001$). In a multivariate logistic regression, liver fibrosis was also associated with alcohol use ($P = 0.004$), higher body mass index ($P = 0.003$), HCV RNA level ($p < 0.001$), and chronic hepatitis B ($P = 0.008$).

Of particular interest were the associations of age and HIV infection with liver fibrosis stage. On average, persons with HIV had liver fibrosis stages comparable to people negative for HIV who were 9.2 years older.

This study provides a comprehensive assessment of liver disease risk factors in a high-risk setting. The finding that liver disease progression occurred at younger ages for people who were positive for HIV was important. Other studies have also tried to examine the relationship of HIV with the age of onset of disease. However, finding appropriate controls who are negative for HIV is always difficult. In this study by Kirk et al, drug users who were positive and negative for HIV were recruited and followed in the same way, and disease was ascertained by the same instrument.

The finding of a strong relationship between HCV viral load and liver fibrosis stage was not expected. In many previous studies, the link between HCV viral load and liver fibrosis stage or development of end-stage liver disease was less or not detected at all. It is possible that those older studies had diminished ability to make those associations because of the narrower linear range of older HCV RNA assays compared to the current, real-time assays. It is also possible that the larger number of persons who could be studied by elastography, or the nature of the elastography measurement itself, compared to liver biopsy, might be significant.

Limitations of the work included the low uptake of HCV treatment in that particular cohort and the cross-sectional nature of the analysis.

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HEPATITIS B AND C INFECTION IN CLINICAL PRACTICE

Spradling PR, Rupp L, Moorman AC, et al; Chronic Hepatitis Cohort Study Investigators. Hepatitis B and C virus infection among 1.2 million persons with access to care: factors associated with testing and infection prevalence. *Clin Infect Dis*. 2012 Oct;55(8):1047-55.

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In this investigation, 1.25 million adults from four private health care organizations were evaluated for chronic viral hepatitis. The study was focused on 867,589 adults who had at least 12 months of continuous followup from January 2006 through December 31, 2008. The median enrollment was 87 months. Investigators further refined their focus to persons with no hepatitis B virus (HBV) or hepatitis C virus (HCV) related code within six months of their first encounter.

Of 866,886 persons without a previous diagnosis, 18.8% were tested for HBV infection, and 1.4% were positive for hepatitis B surface antigen (HBsAg) or HBV DNA. Those who were tested for HBV were more likely to be women, black, or Asian (compared to whites). Associated with having a positive result were being Asian, Native Islander race, or unknown race (all compared to whites).

Among 865,659 people without a previous diagnosis of HCV, 12.7% were tested, and 5.5% of themtested positive. As with HBV, nonwhite racial groups were tested more often for HCV than whites. Age was strongly associated with having a positive HCV test, with an adjusted odds (relative to those < 30 years) of 6.04 for the 50-59 age group and 2.88 for the 40-49 age group.

Investigators also examined whether persons with elevated liver enzymes were tested. Less than half of those with ≥ 2 abnormal alanine aminotransferase (ALT) levels were subsequently tested for HBV or HCV.

Finally, the team extrapolated data from the National Health and Nutrition Examination Studies to a general population of households in the US. Those calculations projected that nearly one-half of HCV and one-fifth of HBV infections in this population were not identified.

This article is important in that it reported on a large number of persons who are actively engaged in routine medical care for seven or more years. Presumably, this population could all receive the benefits of treatment for chronic hepatitis B or C without the barriers of care access. The relatively low rate of testing and failure to detect up to half of all infections is especially significant and points to the potential impact of better screening strategies. The low rate of testing of persons with elevated liver enzymes is especially surprising, given the well-established links between viral hepatitis and those test results.

This study has limitations, in that it is possible that some testing was not indicated (had already been done or was done outside the network), or was not needed. Additional studies are required to determine more effective ways to ensure that appropriate testing is done uniformly in such settings.

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Presented by JHUSOM and IJHN in collaboration with DKBmed.

COMPLETE THE POST-TEST

Step 1.
Click on link to download instructions for the post-test and evaluation

PHYSICIAN POST-TEST

NURSE POST-TEST