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Opportunities for enhanced prevention and control of hepatitis C through improved screening and testing efforts

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Abstract

An estimated 2.4 million people in the United States are living with hepatitis C virus (HCV) infection. In 2020, the Centers for Disease Control and Prevention updated hepatitis C screening recommendations to test adults aged ≥ 18 years at least once in a lifetime and pregnant persons during each pregnancy. For those with ongoing exposure to HCV, periodic testing is recommended. The recommended testing sequence is to obtain an HCV antibody test and, when positive, perform an HCV RNA test. Examination of HCV care cascades has found incomplete HCV testing occurs when a separate visit is required to obtain the HCV RNA test. Hepatitis C core antigen (HCVcAg) testing has been shown to be a useful tool for diagnosing current HCV infection is some settings. Hepatitis C testing that is completed, accurate, and efficient is necessary to achieve hepatitis C elimination goals.

Keywords

Hepatitis C; screening; testing; core antigen

HEPATITIS C EPIDEMIOLOGY

An estimated 2.4 million people in the United States have hepatitis C [1]. There is a bimodal age distribution of reported cases of chronic hepatitis C with the highest number of newly reported infections occurring among persons aged 20-39 years (peak age 33 years) and the second highest number occurring among those aged 55-70 years (peak age 59 years) [2]. Percutaneous exposure is the primary mode of hepatitis C virus (HCV) transmission, and injection drug use (IDU) is the primary risk factor for infection [3]. Sexual transmission of HCV can occur with higher risk behaviors (e.g., condomless, receptive anal intercourse), primarily among persons with HIV [4]. Invasive medical procedures (e.g., injections and hemodialysis) also pose a risk for HCV infection when standard infection control practices are not followed [5,6]. Sharing personal items contaminated with blood (e.g., razors or

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toothbrushes), unregulated tattooing, needlestick injuries among health care personnel, and being born to a mother with hepatitis C are other possible routes of HCV transmission [7].

Hepatitis C can cause liver cirrhosis, and hepatocellular carcinoma, contributing to substantial morbidity and mortality. In 2020, there were an estimated 3.45 hepatitis C-associated deaths per 100,000 cases [2]. With the advent of curative, direct-acting antiviral (DAA) medications, the age-adjusted death rate for hepatitis C has decreased, however, challenges persist as most people are not receiving DAA medications within one year of hepatitis C diagnosis in the United States, even among those who have continuous insurance coverage [8]. Furthermore, Medicaid recipients with hepatitis C are less likely to receive timely treatment compared with those with private insurance, especially if living in states with Medicaid treatment restrictions. Important racial and ethnic disparities are seen in hepatitis C outcomes; the hepatitis C mortality rate is 3.2 times higher among American Indian/Alaska Native persons and 1.8 times higher in non-Hispanic Black persons when compared with non-Hispanic White persons [2].

A rising incidence of acute hepatitis C has been observed in parallel with the opioid crisis and rise in injection drug use. The incidence rate of acute hepatitis C has more than doubled between 2013 and 2020 and is especially high among men, persons aged 20-39 years, those living in the eastern and southeastern United States, and in American Indian/Alaska Native populations [2]. Risk factor information is frequently missing from reports of acute hepatitis C. Among those with risk information reported, 66% of persons with acute hepatitis C report injection drug use. Increasing cases of perinatal HCV infection among exposed infants have also been observed, with 25 states reporting perinatal HCV infection cases during 2020 [2].

HEPATITIS C SCREENING

Chronic hepatitis C is usually asymptomatic and around 40% of all people with hepatitis C are unaware of their infection [9,10]. In 2020, the Centers for Disease Control and Prevention (CDC) updated its recommendations for hepatitis C screening to test adults aged ≥ 18 years at least once in a lifetime and pregnant persons during each pregnancy (except in settings where the prevalence of HCV infection is <0.1%) [3]. The U.S. Preventive Services Task Force (USPSTF) also updated its recommendation to screen all adults aged 18-79 years for hepatitis C [11]. Testing is the first step to accessing curative treatment and interrupting the chain of transmission. For those with ongoing risk factors for exposure to HCV, periodic testing is recommended. The recommended screening frequency varies depending on the population and the exact screening interval for those at ongoing risk of hepatitis C is not known. For those living with HIV, the Department of Health and Human Services guidelines recommend screening at-risk individuals annually or as indicated by risk exposure [12]. The Kidney Disease Improving Global Outcomes (KDIGO), CDC, and National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) all recommend HCV screening every 6 months for persons on maintenance hemodialysis [13–16]. For people who inject drugs, the Infectious Diseases Society of America (IDSA) and American Association for the Study of Liver Diseases (AASLD) guidelines recommend screening at least annually [17]. IDSA/AASLD guidelines recommend annual HCV screening for sexually active HIV-infected adolescent and adult men who have sex with men and HCV

screening at the initiation of HIV pre-exposure prophylaxis (PrEP) and at least annually thereafter [18]. It is recommended to screen all persons detained or incarcerated for hepatitis C at intake into a correctional facility and periodically thereafter for those reporting ongoing risk factors [19]. Guidance regarding hepatitis C diagnostic testing after a known exposure in a health care setting has been published [20]. Hepatitis C screening during each pregnancy allows identification of persons who could benefit from DAA medication during the post-partum period as well as infants who should undergo testing because of perinatal hepatitis C exposure.

HEPATITIS C TESTING

The recommended testing sequence for identifying current HCV infection is to obtain an HCV antibody test and, if positive, perform a nucleic acid test (NAT) for detection of HCV RNA [21]. Detection of HCV RNA confirms current HCV infection and patient counselling and referral for care is warranted. To accomplish both steps of this two-step testing sequence, laboratories can automatically perform a NAT for HCV RNA on any blood sample with a positive HCV antibody or two samples can be obtained initially and, if the HCV antibody is positive, a NAT for HCV RNA detection can be performed on the second sample. Requiring a separate, subsequent patient visit to obtain blood for HCV NAT has been shown to be an unsuccessful strategy and is not cost-effective [22,23]. Examination of HCV care cascades has found that low completion of HCV testing occurs in health care systems that require a separate visit to obtain a NAT for HCV RNA. For example, the Cherokee Nation Health Services implemented measures to improve HCV testing and care among the American Indian/Alaska Native population in northeastern Oklahoma and found that only 68% of the persons who were found to have a positive hepatitis C antibody had the NAT for HCV RNA detection performed [24]. Similarly, data from the Chronic Hepatitis Cohort Study (CHeCS), which includes electronic health record data from 4 participating health systems in the United States, found that 62% of those with a positive HCV antibody had a documented NAT result [25]. The Veterans Health Administration (VA) compared VA facilities that required a separate visit to obtain a blood sample after a positive HCV antibody result with VA facilities that automated the testing (i.e., any HCV antibody positive sample was reflexively sent for HCV RNA) and found that 64% of veterans completed the testing sequence when a separate visit was required versus 98% when the laboratory automated the testing [23]. Finally, the Mid-Atlantic Permanente Research Institute found that implementing a multifaceted HCV care pathway that included automated, laboratory reflex testing for HCV RNA significantly increased the proportion of eligible persons screened and diagnosed with hepatitis C [26].

Another challenge with the current two-step testing sequence is diagnosing recent HCV infection. With a recent HCV infection, there is a period (average 8-11 weeks) before antibody is produced (Figure) [27,28]. During these 2–3 months, infected individuals screened for HCV antibody will test negative. Furthermore, some persons, including those with HIV or otherwise immunocompromised, may take longer to seroconvert [29,30]. For example, one study of a small cohort of HIV-positive men who have sex with men with early HCV infection found that 75% were HCV antibody negative at the time that HCV RNA was detected and 5% remained HCV antibody negative one year later [30]. While CDC

recommends testing for HCV RNA or follow-up testing for HCV antibody in persons who might have been exposed to HCV within the past 6 months, this may be challenging to implement if the ordering clinician is not certain when an HCV exposure occurred [21]. IDSA/AASLD HCV guidance recommends performing a NAT for HCV RNA detection in addition to the HCV antibody when acute HCV infection is suspected due to a reported exposure or clinical presentation, including laboratory findings, of hepatitis [17].

Some persons with HIV take many months or even years to develop a positive antibody after detection of HCV RNA while others may never seroconvert; that is, they have a seronegative chronic HCV infection [30–32]. A combined dataset of samples from the Fat Redistribution and Metabolic Change in HIV infection (FRAM) cohort, the Research and Access to Care for the Homeless (REACH) cohort, an Iowa City HIV clinic cohort, and a Los Angeles HIV clinic identified 37 cases of seronegative HCV infection (out of 1,174 HCV antibody negative samples) yielding a frequency of 3.2% (95% Confidence Interval, 2.2%-4.3%) [33]. Some of the factors associated with HCV RNA positivity in HCV antibody negative persons in this study included injection drug use, lower CD4 cell count (<200 cells/μL) and an elevated alanine aminotransferase (ALT) level. Seronegative HCV infections have also been described in those with end stage renal disease on hemodialysis [34,35].

A different challenge with the current two-step testing sequence occurs when a person is HCV antibody positive and has an undetected HCV RNA test. This scenario can occur either because of spontaneous clearance of the infection, resolution of chronic HCV through antiviral therapy (i.e., achievement of a sustained virologic response, SVR) or because of a false positive HCV antibody. Currently available tests do not allow for differentiation between a false positive HCV antibody and viral clearance. Some persons with this pattern (HCV antibody positive/HCV RNA undetected) may undergo frequent HCV testing (for example, if they are screened regularly due to ongoing risk factors) and therefore repeated HCV antibody testing is done unnecessarily. Wasteful testing in health care settings causes excess cost and drains resources.

STRATEGIES TO IMPROVE HCV TESTING

Hepatitis C testing that is completed, accurate, and efficient is necessary to achieve hepatitis C elimination goals. The World Health Organization (WHO), through the Global Health Sector Strategy on Viral Hepatitis 2016–2021, has called for the elimination of viral hepatitis as a significant public health threat by 2030. One of the four targets to achieve these goals is to diagnose 90% of the HCV-infected population. To achieve adequate screening rates in a population, health care systems should adopt best practices to improve utilization of guideline-adherent, universal HCV screening practices. Using an electronic clinical reminder can significantly improve HCV screening practices in primary care settings [36,37]. For example, an HCV elimination program in the Cherokee Nation included deployment of an electronic clinical reminder in the electronic health record (EHR) and found that 38% of individuals accessing care underwent first-time HCV screening [38]. Since 2003, the Veterans Health Administration has had an EHR HCV screening clinical reminder that has resulted in a highly screened population even before universal HCV screening was recommended by USPSTF and CDC [39]. In 2014, Kaiser Permanente Mid-Atlantic States (KPMAS)

implemented a multi-step, coordinator-supported HCV cascade of testing and care (HCV pathway) to close care gaps and improve HCV screening by utilizing an electronic clinical reminder.

However, clinical reminders in the EHR can become less effective over time as clinicians develop “alert-fatigue” and can even contribute to provider burn-out [40]. Opt-out, default ordering can result in an even higher uptake of HCV screening. Mehta et al. performed a randomized intervention in a hospital setting and found that embedding HCV screening as a default order for screen-eligible patients increased HCV testing compared with a conventional interruptive alert [41]. Direct-to-patient messaging can also be an effective strategy to improve HCV screening and was found to double HCV screening rates when compared with a passive, clinician-facing clinical reminder in one randomized study [42].

While offering HCV testing for persons accessing routine, outpatient primary care has been an effective screening strategy, it is important to recognize the limitations of this strategy to reach all persons. An alternative medical setting that can provide access to HCV screening is emergency departments. Emergency departments (ED) often provide care to persons who may lack access to routine preventive health care services. Numerous studies have demonstrated the effectiveness of HCV testing in EDs but cite the importance of linking those diagnosed with hepatitis C to care after an ED visit [43–45].

CDC, the American College of Obstetricians and Gynecologists and the Society for Maternal-Fetal Medicine recommend hepatitis C screening during each pregnancy [3,46]. Pregnancy is an important opportunity to engage persons in preventive screening and testing for hepatitis C, HIV, hepatitis B, and syphilis, all of which are recommended during pregnancy. Many women only have access to health care during pregnancy and the immediate postpartum period. Identification of HCV infection during pregnancy also can inform pregnancy and delivery management issues that might reduce the likelihood of HCV transmission to the infant. The Society for Maternal-Fetal Medicine recommends a preference for amniocentesis over chorionic villus sampling when needed, and to avoid internal fetal monitoring, prolonged rupture of the membranes, and episiotomy among HCV-infected women, if possible [47]. Hepatitis C screening during pregnancy also allows for identification of infants who should receive HCV testing. Incorporating HCV antibody with reflex to HCV RNA (when the HCV antibody is positive) on the standard obstetric laboratory panel may prove to be a successful way to improve HCV screening during pregnancy.

Hepatitis C screening is an important service for people who use or inject drugs and should be offered in harm reduction settings including syringe service programs and medication assisted therapy clinics. People who use or inject drugs have high rates of hepatitis C with studies showing that 42%–80% have positive HCV antibodies [48]. Innovative models of care have found that treating persons in low-threshold settings and co-locating HCV treatment in a harm reduction setting that provides destigmatizing care can significantly increase rates of successful HCV treatment [49,50].

An estimated 30% of all Americans with hepatitis C experienced incarceration in the prior year [51]. Correctional settings, therefore, can be high-yield settings for diagnosing hepatitis C. In fact, CDC recommends hepatitis C screening for all persons at intake into a correctional or detention setting [19]. However, surveys of state prison systems have found that few prison systems offer universal, opt-out, HCV screening at intake [52]. Other countries, such as the Republic of Georgia and Australia, have demonstrated that HCV testing and treatment in correctional settings are key strategies in reducing HCV incident infections in both correctional and community settings and are necessary to achieve HCV elimination goals.

HCV TESTING: MOVING BEYOND THE CURRENT TWO STEP SEQUENCE

Given the high HCV antibody seroprevalence in some populations, it is important to distinguish current HCV infection from past exposure with viral clearance (i.e., a positive HCV antibody but undetected HCV RNA). Hepatitis C core antigen testing (HCVcAg) testing has been shown to be a helpful and more accessible tool for confirming current HCV infection in some non-US settings. In fact, a pooled analysis of 33 studies found a sensitivity of 94.3% and a specificity of 98.8% when comparing HCVcAg testing with HCV RNA [53]. While this meta-analysis found that HCVcAg is less accurate at detecting viremia when HCV RNA levels are <3,000 IU/mL, it is established that nearly all persons have HCV RNA >1,300 IU/mL at the time of HCV diagnosis [54]. A recent study in the country of Georgia examined three hepatitis C testing strategies at eight different harm reduction sites. For persons with positive hepatitis C antibody on screening, sites could either be assigned to 1) perform an HCV NAT using an on-site Xpert® HCV viral load assay (Cepheid, Sunnyvale, California) or 2) send blood samples to a centralized laboratory for HCVcAg or 3) an HCV RNA test would be performed at designated treatment centers. While treatment uptake was ultimately similar across all three arms, they found that the overall time between screening to treatment initiation was shorter in the arms that used either the on-site Xpert® (median 57 days) and the HCVcAg arms (median 50 days) [55].

HCVcAg can also be useful in detecting seronegative chronic hepatitis C or in recently acquired hepatitis C. One study performed in an outpatient HIV clinic used HCVcAg to identify 15 cases of acute HCV infection in persons with elevated aminotransferases; only 60% had a positive HCV antibody test and would have been missed if the antibody-reliant testing sequence had been used [56]. HCVcAg was also incorporated into an HCV screening algorithm for people on hemodialysis in a Malaysian study and was found to be a cost-effective strategy when used to detect viremia in those with HCV antibodies; if the HCVcAg test was negative, an HCV RNA was performed [57]. One challenge with the HCVcAg assay is that it requires a large, automated platform to be performed on and such platforms are not widely available. Having an HCVcAg that is available in a point-of-care format or as a standalone immunoassay is preferable as this would facilitate greater uptake in a wide variety of settings.

CONCLUSIONS

HCV elimination relies upon the successful identification and treatment of hepatitis C, which in turn depends upon an effective testing approach. Hepatitis C testing strategies need to be flexible to reach people where they are and provide complete results from a single visit. Universal, opt-out HCV testing in primary and obstetric care visits as well as harm reduction settings, emergency departments and correctional settings will lead to major strides in identifying over 90% of persons with HCV infection. Utilizing HCVcAg in testing sequences in populations with either a high HCV antibody seroprevalence or at risk for seronegative HCV infection may improve diagnostic accuracy and be a cost-effective strategy.

Disclaimer:

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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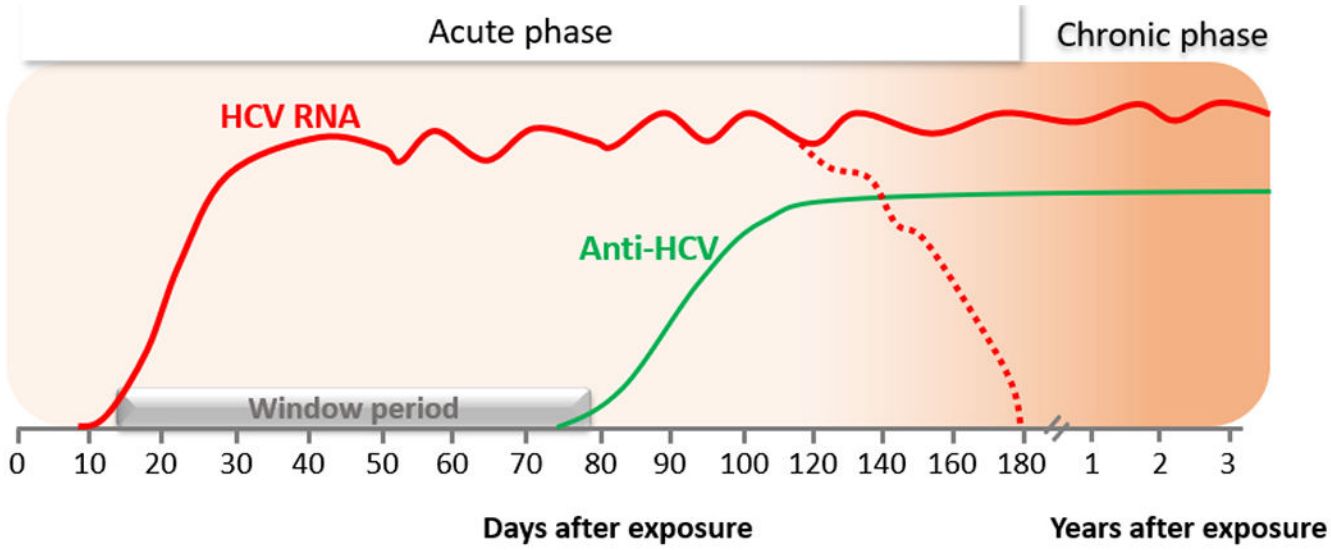

Figure.

Detection of HCV RNA and the appearance of anti-HCV from the time of hepatitis C exposure (in days and years) *

*Figure provided courtesy of Saleem Kamili

Window period: The time between the detection of HCV RNA (red line) and the development of a reactive hepatitis C antibody (anti-HCV, green line).

At the end of the acute phase, the dashed red line illustrates that some persons may experience a decline in HCV RNA to undetectable (i.e., spontaneous clearance). The solid red line into the chronic phase indicates the development of chronic HCV infection.

The anti-HCV is reactive for years even when the HCV RNA is undetectable.

Table.

Hepatitis C screening and testing recommendations for different groups

Group	Hepatitis C Screening Recommendation
All Adults aged ≥18 years	One-time screening (3)
Pregnant persons	Screen with each pregnancy (3)
Persons with HIV	Test at entry to care. Test annually if at ongoing risk (12)
Persons with chronic kidney disease (CKD)	Test at the time of initial CKD evaluation (13,15) Antibody, followed by HCV RNA if positive
Persons receiving in-center maintenance hemodialysis	Test upon initiation of in-center hemodialysis and every 6 months (13-15) HCV RNA alone (13,15) or antibody followed by HCV RNA if positive (13-15)
Persons receiving peritoneal dialysis	Test upon initiation of peritoneal dialysis (13)
Persons receiving home hemodialysis	Test upon initiation of home hemodialysis (13)
Persons on HIV pre-exposure prophylaxis (PrEP)	Test at PrEP initiation and annually thereafter (18)
Correctional settings	Screen all persons at intake. Test periodically if ongoing risk or after an exposure (18)