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## Screening for hepatitis B: Where the CDC and USPSTF diverge

The CDC recently issued guidance on screening for hepatitis B infection. Here's a look at how (and why) these recommendations differ from those of the USPSTF.

The Centers for Disease Control and Prevention (CDC) recently published new recommendations on screening for hepatitis B infection.<sup>1</sup> They recommend screening all adults (ages 18 years and older) at least once.

These recommendations differ in a few ways from those of the US Preventive Services Task Force (USPSTF).<sup>2</sup> This Practice Alert will highlight these differences but also point out areas of agreement between the 2 sets of recommendations—and discuss why 2 separate agencies in the US Department of Health and Human Services reached different conclusions on some issues.

### First, some background on hepatitis B

An estimated 580,000 to 2.4 million people in the United States have chronic hepatitis B (CHB) infection—and as many as two-thirds are unaware of it.<sup>3</sup> In 2020, the Department of Health and Human Services published the Viral Hepatitis National Strategic Plan for the United States with a stated goal of increasing awareness of infection status among those with hepatitis B virus (HBV) from 32% to 90% by 2030.<sup>4</sup> People living in the United States but born outside the country are at highest risk for CHB; they account for 69% of those with the infection.<sup>5</sup>

The incidence of acute HBV infection has declined markedly since the HBV vaccine was recommended for high-risk adults in 1982 and universally for infants in 1991.<sup>6,7</sup> Overall

rates of HBV infection declined fairly steadily starting around 1987—but in 2014, rates began to increase, especially in those ages 40 to 59 years.<sup>8,9</sup> In 2019, 3192 cases were reported; but when one factors in underreporting, the CDC estimates that the number is likely closer to 20,700.<sup>10</sup> This uptick is one reason the Advisory Committee on Immunization Practices changed its HBV vaccination recommendation for adults from a risk-based to a universal recommendation for all unvaccinated adults through age 60 years.<sup>10</sup>

### Chronic hepatitis B infection has serious consequences

The proportion of those infected with HBV who develop CHB differs by age at infection: 80% to 90% if infected during infancy, 30% if infected before age 6 years, and 1% to 12% if infected as an older child or adult.<sup>8</sup>

CHB infection can lead to chronic liver disease, including cirrhosis of the liver, liver cancer, and liver failure. About 25% of those who develop CHB infection during childhood and 15% of those who develop chronic infection after childhood will die prematurely from cirrhosis or liver cancer.<sup>8</sup>

The American Association for the Study of Liver Diseases (AASLD) classifies CHB into 4 phases that reflect the rate of viral replication and the patient's immune response.<sup>11</sup> These phases are:

- immune-tolerant (minimal inflammation and fibrosis)
- hepatitis B e-antigen (HBeAg)-positive immune-active (moderate-

- to-severe inflammation or fibrosis)
- inactive CHB (minimal necroinflammation but variable fibrosis), and
- HBeAg-negative immune reactivation (moderate-to-severe inflammation or fibrosis).<sup>11</sup>

The progression from one phase to the next varies by patient, and not all patients will progress through each phase. The AASLD recommends periodically monitoring the HBV DNA and alanine aminotransferase (ALT) levels in those with CHB to track the progression from one phase to the next and to guide treatment decisions.

### Treatment can be beneficial for those who meet criteria

The evidence report prepared for USPSTF found that antiviral treatment of those with CHB infection resulted in improved intermediate outcomes (histologic improvement, loss of hepatitis B surface antigen [HBsAg], loss of HBeAg, HBeAg seroconversion, virologic suppression, and normalization of ALT levels). The magnitude of benefit varied by location and study design.<sup>12</sup>

In addition, the evidence review found that antiviral therapy was associated with a decreased risk for overall mortality (relative risk [RR] = 0.15; 95% CI, 0.03-0.69), cirrhosis (RR = 0.72; 95% CI, 0.29-1.77), and hepatocellular carcinoma (RR = 0.60; 95% CI, 0.16-2.33). However, these results came from studies that were “limited due to small numbers of trials, few events, and insufficient duration of follow-up.”<sup>12</sup>

The USPSTF and the CDC both judged that the intermediate outcome results, as well as findings that improved intermediate outcomes lead to decreases in chronic liver disease, are strong enough evidence for their recommendations.

However, not all patients with CHB infection require treatment; estimates of patients with HBV infection meeting AASLD criteria for treatment range from 24% to 48%.<sup>1</sup> The AASLD guideline on the treatment of CHB infection is an excellent resource that makes recommendations on the initial evaluation, ongoing monitoring, and treatment decisions for those with CHB.<sup>11</sup>

TABLE 1

## Who’s at heightened risk for hepatitis B infection? A CDC vs USPSTF comparison<sup>1,2</sup>

### Listed by both the CDC and the USPSTF

- People born in countries with HBV prevalence  $\geq 2\%$
- People born in the United States, if not vaccinated against HBV, whose parents were from a country with HBV prevalence  $\geq 8\%$
- Current or former intravenous drug use
- Men who have sex with men
- People with HIV
- Household, needle-sharing, or sexual contacts of people with known HBV infection

### Listed by the CDC and indirectly by the USPSTF

- People on dialysis, hemodialysis, or peritoneal dialysis
- Current and former jail and prison inmates
- People with a history of sexually transmitted infections
- People with a history of hepatitis C virus infection

### Listed by the CDC and not by the USPSTF

- People with a history of multiple sex partners
- People with elevated ALT or AST levels of unknown origin
- Anyone who requests testing

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CDC, Centers for Disease Control and Prevention; HBV, hepatitis B virus; USPSTF, US Preventive Services Task Force.

## How CDC and USPSTF guidance on HBV screening differs

The CDC and USPSTF recommendations for HBV screening differ in 3 aspects: whom to screen, whom to classify as at high risk for HBV infection, and what tests to use for screening.

### Who should be screened?

The USPSTF recommends screening adults and adolescents who are at high risk for HBV. The CDC recommends screening all adults at least once. Both entities agree that those who are at increased risk should be screened periodically, although the optimal frequency has not been established. The USPSTF does not recommend *against* screening for the general population, so universal screening (as advocated by the CDC) is not in direct conflict with the USPSTF’s recommendations.

### Who is at increased risk for HBV infection?

The CDC and the USPSTF differ slightly on the factors they consider to constitute increased

TABLE 2

HBV infection screening test results and recommended actions<sup>1,8,13</sup>

| Clinical state  | Test results   | Patient care action <sup>13</sup>  |
|---|--|--|
| Acute infection   | + HBsAg, total anti-HBc <sup>a</sup> , IgM anti-HBc<br>– Anti-HBs              | Link to HBV infection care   |
| Chronic infection   | + HBsAg, total anti-HBc <sup>a</sup><br>– Anti-HBs, IgM anti-HBc <sup>b</sup>  | Link to HBV infection care   |
| Resolved infection  | + Anti-HBs, total anti-HBc <sup>a</sup><br>– HBsAg, IgM anti-HBc               | Counsel about HBV infection reactivation risk  |
| Immune (immunity inferred from receipt of previous vaccination) | + Anti-HBs <sup>c</sup><br>– HBsAg, total anti-HBc <sup>a</sup> , IgM anti-HBc | Reassure if history of HepB vaccine series completion; if partially vaccinated, complete vaccine series per ACIP recommendations |
| Susceptible, never infected                                     | – HBsAg, anti-HBs <sup>d</sup> , total anti-HBc <sup>a</sup> , IgM anti-HBc    | Offer HepB vaccine per ACIP recommendations  |
| Isolated core antibody positive <sup>e</sup>                    | + Total anti-HBc <sup>a</sup><br>– HBsAg, anti-HBs, IgM anti-HBc               | Depends on cause of positive result  |

ACIP, Advisory Committee on Immunization Practices; anti-HBs, antibody to hepatitis B surface antigen; HBcAg, hepatitis B core antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HepB, hepatitis B; IgG, immunoglobulin G; IgM anti-HBc, immunoglobulin M antibodies to hepatitis B core antigen; total anti-HBc, total antibody to hepatitis B core antigen.

<sup>a</sup> Total anti-HBc is a measure of both IgM and IgG antibodies to HBcAg.

<sup>b</sup> IgM anti-HBc also might be positive in people with chronic infection during severe HBV infection flares or reactivation.

<sup>c</sup> Immune if anti-HBs concentration is > 10 mIU/mL after vaccine series completion.

<sup>d</sup> Anti-HBs concentrations might wane over time among vaccine responders.<sup>8</sup>

<sup>e</sup> Can be the result of a past infection when anti-HBs levels have waned, occult infection, passive transfer of anti-HBc to an infant born to an HBsAg-positive gestational parent, a false-positive, or mutant HBsAg strain that is not detectable by laboratory assay.

risk for HBV infection. These are listed in TABLE 1.<sup>1,2</sup>

The CDC lists 6 categories that the USPSTF does not mention. However, 4 of these categories are mentioned *indirectly* in the USPSTF evidence report that accompanies the recommendations, via statements that certain settings have high proportions of people at risk for HBV infection: sexually transmitted infection clinics; HIV testing and treatment centers; health care settings that target services toward people who inject drugs and men who have sex with men; correctional facilities; hemodialysis facilities; and institutions and nonresidential daycare centers for developmentally disabled persons. People who are served at most of these facilities are also at risk for hepatitis C virus infection.

Three categories are listed by the CDC and not by the USPSTF, in either the recommendation or evidence report. These include a history of multiple sex partners; elevated ALT or aspartate aminotransferase levels of unknown origin; and patient request for testing (because they may not want to reveal risk factors).

**What test(s) should be ordered?**

The USPSTF recommends screening using HBsAg. The CDC recommends using triple-panel screening: HBsAg, anti-hepatitis B surface antigen (anti-HBs), and total antibody to hepatitis B core antigen (anti-HBc).

HBsAg indicates HBV infection, either acute or chronic, or a recent dose of HBV vaccine. Anti-HBs indicate recovery from HBV infection, response to HBV vaccine, or recent receipt of hepatitis B immune globulin. Total anti-HBc develops in all HBV infections, resolved or current, and usually persists for life. Vaccine-induced immunity does not cause anti-HBc to develop.

The USPSTF's rationale is that testing for HBsAg is more than 98% sensitive and specific for detecting HBV infections.<sup>2</sup> The CDC recommends triple testing because it can detect those with asymptomatic active HBV infections (this would be a rare occurrence); those who have resolved infection and might be susceptible to reactivation (eg, those who are immunosuppressed); and those who are susceptible and need vaccination.

Interpretation of HBV test results and suggested actions are described in TABLE 2.<sup>1,8,13</sup>

### Why do the CDC and USPSTF differ?

While it would be optimal if the CDC and the USPSTF coordinated and harmonized recommendations, this is difficult to achieve given their different missions. The USPSTF is charged to make evidence-based recommendations about preventive services such as screenings, behavioral counseling, and preventive medications, which are provided by clinicians to individual patients. The Task Force uses a very strict evidence-based process and will not make recommendations unless there is adequate evidence of efficacy and safety. Members of the Task Force are primary care professionals, and their collaborating professional organizations are primary care focused.

The CDC takes a community-wide, public health perspective. The professionals that work there are not always clinicians. They strive to prevent as much illness as possible, using public health measures and making recommendations to clinicians. They collaborate with professional organizations; on topics such as hepatitis and other infectious diseases, they collaborate with specialty-oriented societies. Given the imperative to act with the best evidence available, their evidence assessment process is not as strict.

The result, at times, is slight differences in recommendations. However, the HBV screening recommendations from the CDC and the USPSTF agree more than they do not. Based on practice-specific characteristics, family physicians should decide if they want to screen all adults or only those at increased

risk, and whether to use single- or triple-test screening.

JFP

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➤ Based on practice-specific characteristics, family physicians should decide if they want to screen all adults or only those at increased risk, and whether to use single- or triple-test screening.

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