



Screening and Diagnosis of Hepatitis B Virus (HBV) Infection

SYNOPSIS AND RELEVANCE

Multiple tests are available for the diagnosis of acute and chronic hepatitis B virus (HBV) infection as well as for evaluating immune status. Selecting the most appropriate serologic and antigenic markers along with properly interpreting results can be complex and confusing, especially for the non-specialist. Laboratory guidance and interventions to assist with optimal test selection and interpretations can reduce unnecessary or incomplete testing as well as reduce risk for diagnostic errors. The objective of this module is to assist with optimizing test ordering and reporting practices involving markers used for initial evaluation of HBV infection based on specific clinical indications. This module will not address hepatitis B testing for managing and treating patients with known HBV infections.

INSIGHTS

1. Due to the variety of HBV markers, test selection can be complex and lead to more testing than necessary. Similarly, incomplete evaluations may potentially cause misinterpretation and a poor diagnostic outcome. In particular, testing practices that involve use of a general “hepatitis B virus panel” with various serologic and antigenic HBV tests can lead to over or under testing as well as difficulty in interpreting results for the non-specialist. Alternatively, use of specific hepatitis B screening protocols for distinct clinical indications, together with reporting relevant comments for test interpretation is strategy for achieving more optimal diagnostic outcomes.
2. Serum alanine aminotransferase (ALT) levels could be used as an indirect method for differentiating asymptomatic (normal ALT) from symptomatic (elevated ALT) testing indications.
3. For high-risk asymptomatic patients (normal ALT):
 - a. Optimized testing would include hepatitis B surface antibody (anti-HBs) for all cases, and an additional (reflex) hepatitis B surface antigen (HBsAg) test when anti-HBs is negative.
 - b. Alternatively, both anti-HBs and HBsAg would indicate acceptable, but less optimal testing strategy than reflex panel.
 - c. Cases in which anti-HBs is not tested, or HBsAg is not tested when anti-HBs is negative, would indicate under-testing.
 - d. Cases in which total immunoglobulin to hepatitis B core antibody (anti-HBc) or immunoglobulin M to hepatitis B core antibody (anti-HBc, IgM), or hepatitis B virus DNA (HBV DNA) are ordered indicate over-testing.
4. For symptomatic patients (elevated ALT):
 - a. Optimized testing would include both anti-HBs and anti-HBc, total for all cases, and an additional HBsAg and anti-HBc, IgM test for patients with positive anti-HBc is positive and negative anti-HBs results
 - b. Alternatively, testing anti-HBs, anti-Hc (total and IgM), and HBsAg, without reflex testing is less optimal.
 - c. Cases in which either anti-HBs and/or anti-HBc are not ordered would indicate under-testing.
 - d. Cases in which anti-HBc is positive but not followed up with HBsAg and anti-HBc, IgM, would indicate under-testing.

BACKGROUND

Hepatitis B virus (HBV) is a blood-borne pathogen that is transmitted from either 1) infected mother to child during pregnancy or at birth, 2) percutaneously, or 3) sexually. While blood transfusion is another mode of infection, screening donors by HBV nucleic acid testing has reduced risk to only 1 in 1 million transfusions.¹ It is estimated that there are about 20,000 new cases of HBV infection each year in the United States.² This leads to chronic infection in about 5% of adults and up to 10-60% in infants not given HBV immune globulin and vaccinated at birth.^{3,4} Routine vaccination for HBV in infants has reduced the incidence of disease and will lead to many fewer cases in the future.

Indications for Testing

There are three primary clinical indications to test for hepatitis B infection. These include: 1) asymptomatic high-risk patients, 2) symptomatic patients with evidence of acute or chronic liver disease, and 3) patients who may be at risk for reactivation of HBV infection prior to receiving certain immunosuppressive medications. It is important to differentiate between these indications, since this informs the specific tests that should be utilized.

1. Asymptomatic High-Risk Patient Panel

Testing for HBV infection in asymptomatic patients is recommended for certain high-risk groups, regardless of prior immunization history. This group includes individuals born in geographical areas with high HBV infection rates (eg, Western Africa, Eastern Europe, Southeast Asia), pregnant women, individuals with known HIV or hepatitis C infections, men who have sex with men, those with multiple sexual partners or history of sexually transmitted disease, household contacts of those with chronic HBV infection, dialysis patients, incarcerated adults, those with various types of chronic liver disease, and groups with occupational (eg, healthcare workers) or other exposure risks (eg, international travel).

A diagnostic strategy for this group may include initial testing for hepatitis B surface antibody (anti-HBs) to check for immunity (from vaccine or natural infection), and if seronegative, followed by hepatitis B surface antigen (HBsAg) to check for possible chronic infection (positive HBsAg). Asymptomatic patients positive for only HBsAg should be retested in 6 months. Persistent of HBsAg is consistent with chronic infection, while seroconversion (positive anti-HBs) is consistent with immunity after recent HBV infection.

Table 1

High Risk, Asymptomatic Patient	Anti-HBs	Reflex HBsAg	Interpretive Comments
	POS	None	Immunity to Hepatitis B
	NEG	NEG	Non Immune, consider vaccination
POS		Consistent with chronic infection, repeat panel in 6 months	

2. Symptomatic Patient Panel with Suspected Liver Disease

Testing for both acute and chronic hepatitis B infection should be considered for symptomatic patients with elevated serum transaminase or other findings associated with acute or chronic hepatitis. An optimal testing strategy for this group involves an initial panel of 2 tests which includes both hepatitis B core total antibodies (anti-HBc) and anti-HBs. Specimens which test positive for anti-HBc and negative for anti-HBs should undergo reflex testing with IgM antibody to hepatitis B core antigen (anti-HBc IgM) and HBsAg to aid in differentiating acute from chronic HBV infection.

In some cases, anti-HBc is the only positive hepatitis B marker. This “solitary anti-HBc” pattern is non-diagnostic. Follow up testing with HBV DNA, which requires a new specimen, is needed to differentiate occult HBV infection (positive HBV DNA) from other conditions associated with this serologic pattern. If HBV DNA is negative, the patient can be offered vaccination with follow up testing after last dose for anti-HBs to distinguish chronic infection (negative anti-HBs) from immunity (positive anti-HBs).

Table 2

Symptomatic (hepatitis) Patient	Panel Tests		Reflex Tests		Interpretive Comments
	Anti-HBs	Anti-HBc	Anti-HBc, IgM	HBsAg	
	NEG	NEG	None		Non-immune, consider HBV vaccination
	POS	NEG	None		Immunity to Hepatitis B
	POS	POS	None		Immunity to Hepatitis B from past infection
	NEG	POS	NEG	NEG	Solitary anti-HBc pattern; non-diagnostic - HBV DNA testing recommended
			NEG	POS	Consistent with chronic infection, repeat panel in 6 months
			POS	NEG	Consistent with acute hepatitis B infection
			POS	POS	

3. HBV Reactivation Risk Panel

Screening for past exposure to hepatitis B is recommended for individuals with planned treatment for hepatitis C or receiving certain chemotherapeutic or immunosuppressive agents (eg, rituximab). These agents may cause HBV reactivation in previously infected immune individuals that requires antiviral prophylaxis. A panel of 2 tests including anti-HBc and HBsAg are recommended for these patients. If either anti-HBc or especially HBsAg are positive, follow up testing with HBV DNA and other markers such as hepatitis B e-antigen (HBeAg) and hepatitis B e-antibody (anti-HBe) are recommended. Adding an additional specimen for potential HBV DNA reflex testing may be considered for patient convenience.

Table 3

	Panel Tests		Reflex	Interpretive Comments
	Anti-HBc	HBsAg	HBV DNA	
HBV Reactivation Screen	NEG	NEG	None	Low risk for reactivation; consider HBV vaccination if anti-HBs negative
	POS	NEG	NEG	Past infection, low to moderate (anti-CD20 Rx) risk for reactivation
	POS	NEG	POS	Occult HBV infection, moderate risk for reactivation
	POS	POS	<10 ⁵ copies/mL	Chronic HBV infection; high risk for reactivation
	POS	POS	>10 ⁵ copies/mL	Chronic HBV infection; highest risk for reactivation
	NEG	POS	Defer	Rare, atypical pattern, recommend retesting for confirmation

Abbreviation: Rx, drug treatment

Hepatitis B Tests

Anti-Hepatitis B Surface Antigen (Anti-HBs)

This antibody, when present in individuals who are also positive for anti-HBc indicates immunity to HBV from past infection. The presence of anti-HBs, alone, in the absence of anti-HBc indicates immunity. Combining anti-HBs with anti-HBc as a panel for initial evaluation of symptomatic patients with acute or chronic hepatitis can be a useful diagnostic testing strategy as described above.

Hepatitis B Core Total Antibodies (Anti-HBc, also Anti-HBc, Total)

This test includes both IgG and IgM antibodies against hepatitis B core antigen. A positive result, while not specific for type of HBV infection (eg, acute, chronic, or past infection with immunity) indicates exposure to HBV. Less often, some reactive anti-HBc results are found to be false positives. Importantly, a negative anti-HBc serologic result is strong evidence against ever being exposed to HBV since false negative results are extremely rare. HBV vaccine which only contains recombinant surface antigen (HBsAg) does not elicit an anti-HBc response. Anti-HBc testing is indicated when acute or chronic HBV infection is suspected. It is also recommended for evaluation of patients at risk for HBV reactivation prior to immunosuppressive therapy.

IgM Antibody to Hepatitis B Core Antibody (Anti-HBc, IgM)

The presence of anti-HBc, IgM, indicates acute HBV infection.

Hepatitis B Surface Antigen (HBsAg)

The presence of HBsAg indicates either acute (with positive anti-HBc, IgM) or chronic HBV infection. The persistence of HBsAg for 6 months or longer is diagnostic for chronic HBV infection. HBsAg may also be transiently present for a few weeks after receiving a dose of HBV vaccine.

HBV DNA

Solitary Anti-HBc Pattern

Solitary anti-HBc is a serologic pattern characterized by the following combination of HBV test results: 1) positive anti-HBc, 2) negative anti-HBs, 3) negative anti-HBc, IgM, and 4) negative HBsAg. This pattern is non-diagnostic and can be seen in various conditions including, occult chronic infection, immunity, or may represent a false positive anti-HBc result. In this setting, testing for HBV DNA is important since a positive result indicates occult chronic infection. This test is particularly important in patients with solitary anti-HBc and planned treatment with therapeutic agents that increase risk for reactivation of HBV infection. Patients with solitary anti-HBc pattern that test negative for HBV DNA can be further evaluated, if needed by anti-HBs response four weeks after last dose of HBV vaccine. A seropositive anti-HBs response indicates immunity to HBV, while lack of anti-HBs response is consistent with chronic infection (HBV negative occult infection).

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