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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.

OBJECTIVES

1. Develop an optimal diagnostic testing strategy for initial diagnosis for hepatitis B infection.
2. Promote informative interpretation of HBV test results that reduces risk for diagnostic error.

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 human immunodeficiency virus (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 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 hepatitis B virus DNA (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, anti-CD20 antibodies [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 Immunoglobulin M (IgM) and Immunoglobulin G (IgG) 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).



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 anti-HBs for all cases and an additional (reflex) 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 anti-HBc (IgM and/or total) or 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-HBc (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.

INTERVENTIONS

1. Develop consensus HBV testing preferences and guidelines endorsed by stakeholders (eg, gastroenterologists, infectious disease specialists). This should also include frequency of testing (eg, once per year).
2. Consider offering specific screening panels based on intended use, eg, asymptomatic, symptomatic, reactivation risk (see **Tables 1-3**). For example, **Table 2** shows HBV testing algorithm for symptomatic individuals that includes a two-stage reflex testing protocol that optimizes testing. The first stage in which only anti-HBc and anti- HBs are tested will provide a diagnosis in most cases. The few remaining individuals who are seropositive for anti-HBc, would then benefit from further evaluation with anti-HBc, IgM and HBsAg.
3. Operationalize the preferred general HBV screening protocols with descriptive names and ordering comments (if necessary) based on screening indications. These panels should be intended for the non-specialist to guide and optimize testing.
4. Attempt to eliminate unnecessary bundled HBV panels that include multiple various markers that are simultaneous tested but not aligned with endorsed testing protocols.
5. Consider adding the preferred general HBV screening panel (symptomatic and/or asymptomatic) to a general viral hepatitis panel, which may include, for example anti-hepatitis C and/or anti-hepatitis A antibodies based on consensus of stakeholders.
6. It may be helpful to provide specific diagnostic guidance as a comment on the report based on the patten of results at various stages of testing as shown in the table if supported by health information system.
7. Consider designating a pathologist or other specialist who would be available to offer further HBV interpretive or testing advice with contact information on report.
8. Check for hepatitis B markers or panels included in general order panels (eg, admission, pre-op) that may cause unnecessary repeat testing.
9. Check for specific hepatitis B markers (eg, HBeAg, anti-HBe, or HBV DNA) that are ordered by non-specialists (eg, primary care or nurse practitioners) that may indicate test selection problems.



INTERVENTION ANALYSIS

1. Monitor the volume of various hepatitis B markers ordered individually compared to those ordered as part of preferred panel. Exclude specialists (eg, gastroenterologists) who treat patients with hepatitis B, since a substantial amount of testing may be for disease management (eg, HBV DNA, HBe antigen or antibody) rather than for screening.
2. Before interventions are initiated, review specific screening panels and reflex tests based on intended use, eg, asymptomatic, symptomatic (see **Appendix A**). Serum 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 (normal ALT) patients, record the number of various HBV markers including anti- HBs, anti-HBc, total, anti-HBc, IgM and HBsAg:
 - a. Record cases in which anti-HBs is not tested, or HBsAg is not tested when anti-HBs is negative which would indicate under-testing.
 - b. Record cases in which anti-HBc (IgM and/or total) or HBV DNA are ordered which would indicate over- testing.
4. For symptomatic (elevated ALT) patients, record the number of various HBV markers including anti-HBs, anti- HBc, total, anti-HBc, IgM and HBsAg following panel and reflex testing cases:
 - a. Record cases in which either Anti-HBs and/or anti-HBc are not ordered which would indicate under-testing.
 - b. Record cases in which anti-HBc is positive but not followed up with HBsAg and anti-HBc, IgM, which would indicate under-testing.

APPENDICES

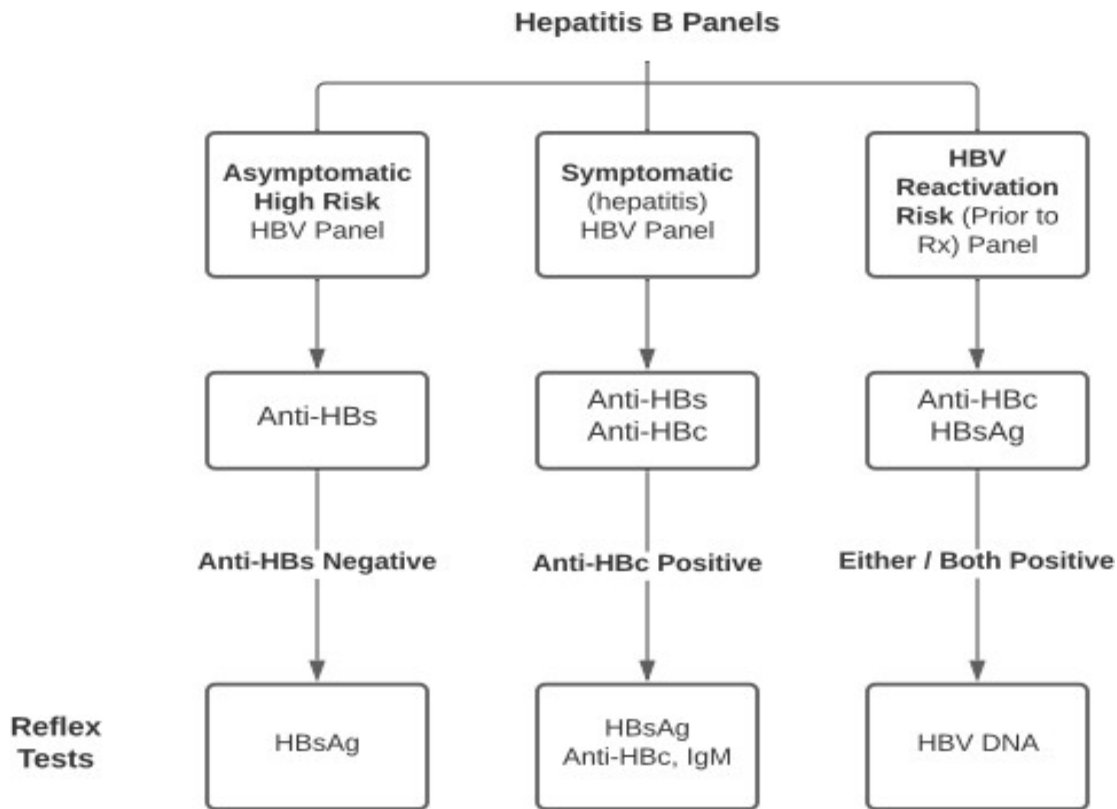
APPENDIX A: PRE-INTERVENTION ASSESSMENT

Pre-Intervention (use a selected time period, eg, 3 months):	
For high risk asymptomatic (normal ALT) patients, the number of cases in which anti- HBs is not tested, or HBsAg is not tested when anti-HBs is negative (under-testing)	A1
For high risk asymptomatic (normal ALT) patients, the number of cases in which anti- HBc (IgM and/or total) or HBV DNA are ordered (over-testing)	A2
For symptomatic (elevated ALT) patients, the number of cases in which either Anti- HBs and/or anti-HBc are not ordered (under-testing)	A3
For symptomatic (elevated ALT) patients, the number of cases in which anti-HBc is positive but not followed up with HBsAg and anti-HBc, IgM (under-testing)	A4
Total markers undertested	(A1+A3+A4) = A5

APPENDIX B: POST INTERVENTION ASSESSMENT

Post-Intervention (use same time period as above, eg, 3 months)	
For high risk asymptomatic (normal ALT) patients, the number of cases in which anti- HBs is not tested, or HBsAg is not tested when anti-HBs is negative (under-testing)	B1
For high risk asymptomatic (normal ALT) patients, the number of cases in which anti-HBc (IgM and/or total) or HBV DNA are ordered (over-testing)	B2
For symptomatic (elevated ALT) patients, the number of cases in which either Anti- HBs and/or anti-HBc are not ordered (under-testing)	B3
For symptomatic (elevated ALT) patients, the number of cases in which anti-HBc is positive but not followed up with HBsAg and anti-HBc, IgM (under-testing)	B4
Total markers undertested	(B1+B3+B4) = B5
Percent change in test volume for undertesting	$\frac{(B5 - A5)}{A5} \times 100\% = B6$
Percent change in test volume for over-testing	$\frac{(A2 - B2)}{A2} \times 100\% = B7$

APPENDIX C: EXAMPLE OF A HEPATITIS B TESTING ALGORITHM



QUESTIONS AND ANSWERS QUESTION 1

OBJECTIVE

Understand the serologic characteristic of occult hepatitis B and importance of follow up testing for HBV DNA to help resolve diagnostic significance of the solitary anti-HBc pattern.

QUESTION 1

Hepatitis B testing was performed on a 44-year-old male with mildly elevated serum alanine aminotransferase (ALT) levels which have persisted for 12 months. Prior testing 6 months ago showed seropositive results for anti-HBc, total only; with negative results for both anti-HBs, HBsAg and anti-HBc, IgM. Repeat testing included HBV DNA and showed the following results:

<u>Test</u>	<u>Result</u>
Anti-HBs:	Negative
HBsAg:	Negative
Anti-HBc (total):	Positive
HBV DNA	Positive

These findings are most consistent with:

- A. Acute Hepatitis B
- B. Chronic Active Hepatitis
- C. Occult Chronic Hepatitis B
- D. Past infection with immunity
- E. Solitary anti-HBc, non-diagnostic

The correct answer is C, occult hepatitis B infection. Chronic hepatitis B infection is typically associated with seropositive anti-HBc results along with persistent of HBsAg for at least 6 months. Occult hepatitis B is a less common form of chronic hepatitis B infection in which only HBV DNA is detected without HBsAg

A is incorrect. Acute hepatitis B is a transient condition. Persistence of elevated ALT levels for one year and prior history (6 months ago) of positive anti-HBc, indicating past HBV infection, is inconsistent with acute infection.

B is incorrect. Chronic active hepatitis is a non-specific term that typically applies to hepatic injury secondary to autoimmune disorders, drug toxicity or chronic hepatitis C infection

D is incorrect. While the presence of anti-HBc indicates past infection, the absence of anti-HBs and presence of HBV DNA indicate chronic infection rather than immunity.

E is incorrect. While only seropositive for anti-HBc (negative for HBsAg and anti-HBs), the history of persistently elevated ALT and positive HBV results is diagnostic for occult chronic hepatitis B.

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QUESTION 2

Understand the principles of prerequisite hepatitis B testing for certain immunosuppressive treatments that increase risk of HBV reactivation disease.

QUESTION 2

A 48-year-old female with severe rheumatoid arthritis is being evaluated for rituximab therapy. Prior to treatment the following tests are performed: Anti-HBs, Anti-HBc, HBsAg, anti-hepatitis C virus, HIV antibody, quantitative immunoglobulin, and serum protein electrophoresis and liver panel. All test results are seronegative or within reference interval except for reactive (positive) anti-HBc antibody. Which of the following statements is correct about risks to patient from rituximab treatment?

- A. Test results are consistent with immunity to hepatitis B, no risk from rituximab treatment.
- B. Test results indicate chronic hepatitis B infection, contraindication to treat with rituximab.
- C. Test results are inconclusive, follow up with additional HBV tests including HBV DNA.
- D. Test results are inconclusive, follow up with HBV vaccination before treatment with rituximab.
- E. Test results indicate high risk for HBV reactivation; HBV anti-viral treatment should be administered before starting rituximab.

The correct answer is C. A positive test for anti-HBc suggests prior exposure to hepatitis B even when neither anti-HBs or HBsAg are reactive. HBV DNA should be tested to check for chronic, occult HBV infection which, if present, would increase risk for reactivation disease and require close monitoring during treatment with rituximab. Absence of HBV DNA would indicate less risk for reactivation. It is also possible that anti-HBc is a false positive result and either repeating the test for confirmation and/or vaccinating the patient before rituximab could be considered.

A is incorrect. Anti-HBc indicates past exposure to HBV, but not necessarily immunity. Since anti-HBs is non-reactive, there is no laboratory evidence that the patient has immunity to HBV.

B is incorrect. Anti-HBc as the only positive marker may indicate chronic HBV infection, however, this finding (solitary anti-HBc) is non-diagnostic and may also be seen with acute hepatitis B, immunity or possibly a false positive result.

D is incorrect. It is correct that test results are inconclusive, but vaccination is not correct course of action. A seropositive anti-HBc test indicates past exposure to HBV, so vaccine would likely not be of any benefit to patient. The next step is to test for HBV DNA (and possibly HBeAg and Anti-HBe) as additional tests for chronic or occult HBV infection. If all these tests are negative, it is possible that anti-HBc was a false positive. A repeat anti-HBc and/or vaccine may be beneficial to resolve that issue and determine the immune status of patient before treatment with rituximab.

E is incorrect. While a seropositive test result for anti-HBc indicates past exposure to HBV, in the absence of HBsAg, the result does not pose a high enough risk for reactivation disease that would warrant prophylactic anti-viral treatment. Further testing with HBV DNA before and during treatment with rituximab is indicated.

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QUESTION 3 OBJECTIVE

Understand test(s) to order to confirm diagnosis of a chronic hepatitis B.

QUESTION 3

A 38-year-old incarcerated male with history of injection drug use, persistently elevated serum ALT levels and chronic hepatitis C for which he has declined treatment was evaluated for hepatitis B. Prior testing several years ago was negative for both anti-HBs and HBsAg tests ago. Follow up testing for hepatitis B now shows positive reactivity for HBsAg with seronegative results for anti-HBs. Reflex testing for anti-HBc, IgM was negative.

Further testing should include:

- A. HBV DNA
- B. Anti-HBc, total
- C. HBsAg in 6 months
- D. HBV DNA in 6 months
- E. No further testing indicated.

The correct answer is C. Seroconversion from negative to positive HBsAg without evidence for acute infection (negative anti-HBc, IgM) or immunity (negative anti-HBs) suggests chronic HBV infection. However, persistence of HBsAg for 6 months or longer is needed to confirm diagnosis.

A is incorrect. While HBV DNA is likely to be positive, this would not provide additional diagnostic information. It might be helpful as baseline test prior to treatment; however, patient had declined treatment for HCV infection as well as HBV vaccination (prior to infection).

B is incorrect. Anti-HBc, total would almost certainly be positive due to HBV infection as shown by HBsAg seroconversion. However, it would not be necessary for diagnosis.

D is incorrect. Persistence of HBsAg rather than HBV DNA for at least six months is recommended to confirm diagnosis of chronic hepatitis B infection.

E is incorrect. While there is strong laboratory evidence of chronic HBV infection due to HBsAg seroconversion and lack of immunity (negative anti-HBs), confirmation requires retesting for HBsAg in 6 months to demonstrate persistence.

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