Interpretation and Differentiation of Isolated Positive Hepatitis B Core Antibody

Most hepatitis B virus (HBV) triple panel screening (HBsAg, anti-HBs, total anti-HBc; see definitions below) results have a single interpretation with recommended action and next steps[a]; however, an isolated positive total anti-HBc laboratory result (HBsAg negative, anti-HBs negative, total anti-HBc positive) may have multiple interpretations [Table].

It is important to distinguish between the different scenarios because clinical management, transmission risk, and long-term health outcomes vary widely.

Persons with isolated positive total anti-HBc test results should have their immune status and risk history considered before deciding next steps. Further, the interpretation of an isolated positive total anti-HBc laboratory result also depends on endemicity in the region where the person was born. For example, for people born in or from regions where there is low prevalence of HBV infection, such as the United States, an isolated positive total anti-HBc test may be a false-positive result. In contrast, for people who were born in or from countries where HBV infection is endemic (i.e., most countries in southeast Asia and sub-Saharan Africa), an isolated positive total anti-HBc test result may indicate 1) previous infection with loss of anti-HBs, 2) occult infection, or 3) chronic infection with mutant HBsAg.

National Health and Nutrition Examination Survey (NHANES) 2013-2018 data were used to estimate:

- 0.9% of the US population[b] or 2.3 million persons had isolated positive total anti-HBc[1].
- 0.6% of persons born in the United States had isolated positive total anti-HBc, and 2.1% of non-US-born persons had isolated positive total anti-HBc[1].

Definitions

Hepatitis B surface antigen (HBsAg):

A protein on the surface of HBV that can be detected in high levels in serum during acute or chronic HBV infection. The presence of HBsAg indicates the person is infectious, except when it appears transiently positive within 30 days[c] after a dose of hepatitis B (HepB) vaccine. Production of antibodies to HBsAg is part of a normal immune response to hepatitis B vaccination or infection with hepatitis B virus. HBsAg is the antigen used in the HepB vaccine.

Antibody to hepatitis B surface antigen (anti-HBs):

The presence of anti-HBs may indicate immunity either from resolved HBV infection or successful/complete hepatitis B vaccination. The appearance of anti-HBs after the loss of HBsAg indicates recovery from HBV infection. Anti-HBs also develops in a person who has been successfully vaccinated against HBV. Among vaccine responders who complete a HepB vaccine series, anti-HBs levels can wane over time; however, the majority have immune memory and will mount a protective immune response if exposed to HBV.

Total antibody to hepatitis B core antigen (total anti-HBc):

The presence of total anti-HBc indicates exposure to HBV and appears at the onset of symptoms in acute HBV infection. Total anti-HBc is a measure of both IgM and IgG antibodies together; IgM anti-HBc often becomes undetectable within 6 months after infection, IgG alone generally indicates infection >6 months prior and will persist for life. People who are vaccinated against HBV but never infected with HBV, do not develop antibodies to hepatitis B core antigen.

Table. Clinical scenarios that can cause an isolated positive total anti-HBc result (HBsAg negative, anti-HBs negative, total anti-HBc positive)

Scenario	Additional Information	Action Step
Occult HBV infection *(Defined as "the presence of HBV covalently closed circular DNA in the liver or HBV DNA in the blood of persons who test negative for HBsAg"[1])*	• HBV DNA detectable • No response to HepB vaccination • HBsAg can be present in small amounts but below the level of detection by commercially available HBsAg assays[6] or may be masked by non-neutralizing circulating anti-HBs antibodies	Link to hepatitis B care; at risk for flare during hepatitis C treatment, or if immunocompromised by medications or condition
Chronic HBV infection with a variant HBV strain containing mutations in HBsAg protein[d]	• HBV DNA detectable • HBV infection despite appropriate vaccination and immune response • HBsAg may be detectable by specific assays capable of detecting commonly occurring HBsAg variants with surface antigen mutations[e]	Link to hepatitis B care; at risk for flare during hepatitis C treatment, or if immunocompromised by medications or condition
Resolved HBV infection with waning anti-HBs levels	• HBV DNA undetectable • Challenge[f] vaccine dose will result in detectable and seroprotective levels of anti-HBs	Remains at risk for HBV reactivation if immunocompromised by medications or condition
False positive total anti-HBc	• HBV DNA undetectable • Response to the HepB vaccination series (i.e., detectable seroprotective[g] levels of anti-HBs) • May be seen with heterophile antibodies[h] or other interfering substances • May be due to laboratory error • Repeat testing of total anti-HBc using a second serum sample, ideally with a different assay, may yield negative result	Complete HepB vaccine series if not previously vaccinated per ACIP recommendations[3]
Passive transfer of total anti-HBc to an infant born to an HBsAg-positive gestational parent	• HBV DNA undetectable • Resolution of the positive total anti-HBc expected after 24 months of age	Complete HepB vaccine series including birth dose and HBIG per ACIP recommendations[4] Post-vaccination serologic testing is recommended and should include testing for HBsAg to determine whether the infant is infected, and for antibody to hepatitis B surface antigen (anti-HBs) to assess immune response/status at 9-12 months of age
Serologic "window period"[i]	• HBV DNA may be detectable • Recent laboratory results may reveal transaminitis (abnormal liver enzymes), positive HBsAg, positive IgM anti-HBc, or detectable HBV DNA • Recent clinical, subclinical, or asymptomatic acute HBV infection	Anti-HBs can be rechecked in 2-3 months to assess recovery from acute infection

[a] https://www.cdc.gov/hepatitis-b/hcp/diagnosis-testing/index.html

[b] Noninstitutionalized population in the United States (National Health and Nutrition Examination Survey (NHANES) - Health, United States)

[c] Transient HBsAg positivity can occur up to 52 days following vaccination among hemodialysis patients.

Calisti G, Herman O, Powley M, Haque T. Persistence of hepatitis B surface antigen in blood in a chronic haemodialysis patient following vaccination booster. BMJ Case Rep. 2014;2014:bcr2013202191. Published 2014 Jun 10. doi:10.1136/bcr-2013-202191

[d] Mutant HBV isolates can have mutations in the major hydrophilic region of the S protein and may not be detected by all HBsAg assays.

Coppola N, Onorato L, Minichini C, et al. Clinical significance of hepatitis B surface antigen mutants. World J Hepatol. 2015;7(27):2729-2739. doi:10.4254/wjh.v7.i27.2729

Shi Y, Wei F, Hu D, et al. Mutations in the major hydrophilic region (MHR) of hepatitis B virus genotype C in North China. J Med Virol. 2012;84(12):1901-1906. doi:10.1002/jmv.23419

Zhang K, Liu Y, Chen R, et al. Antigenicity reduction contributes mostly to poor detectability of HBsAg by hepatitis B virus (HBV) S-gene mutants isolated from individuals with occult HBV infection. J Med Virol. 2018;90(2):263-270. doi:10.1002/jmv.24936

[e] At the time of drafting this content, two FDA approved assays are available that can detect most commonly occurring HBV mutants (the Abbott ARCHITECT HBsAg assay and Siemens Centaur HBsAg II assay).

[f] Challenge dose is an additional vaccine dose administered after loss of anti-HBs in a vaccinated individual. A challenge dose may induce an "anamnestic response" resulting in high seroprotective levels of antibodies to hepatitis B surface antigen.

Schillie S, Vellozzi C, Reingold A, et al. Prevention of Hepatitis B Virus Infection in the United States: Recommendations of the Advisory Committee on Immunization Practices. MMWR Recomm Rep 2018;67(No. RR-1):1–31. doi: 10.15585/mmwr.rr6701a1

[g] "Anti-HBs levels of ≥10 mIU/mL are generally considered seroprotective; however, different assays have different assay cutoff values based on which reported levels of anti-HBs might vary depending on the assay used. Refer to the package insert of the test for the determination of actual/correct levels of anti-HBs antibodies."

Schillie S, Vellozzi C, Reingold A, et al. Prevention of Hepatitis B Virus Infection in the United States: Recommendations of the Advisory Committee on Immunization Practices. MMWR Recomm Rep 2018;67(No. RR-1):1–31. doi: 10.15585/mmwr.rr6701a1

[h] Heterophile antibodies are "a group of antibodies that are poorly defined and react with a wide spectrum of antigens" that interfere with immunoassays.

Miller J, Levinson S. Interferences in Immunoassays in: Diamandis E, Christopoulos T, ed. Immunoassay. Academic Press; 1996: 165-190. https://doi.org/10.1016/B978-012214730-2/50008-X

[i] Serologic "window period between HBV infection and detection of HBsAg [is] estimated to be around 38 days but depends on analytical sensitivity of assay used, immunocompetence of host and individual virus

WHO Guidelines on Hepatitis B and C Testing. Geneva: World Health Organization; 2017 Feb. TABLE 4.2, Summary of markers of HBV infection. Available from: https://www.ncbi.nlm.nih.gov/books/NBK442290/table/ch4.t2/

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11. WHO Guidelines on Hepatitis B and C Testing. Geneva: World Health Organization; 2017 Feb. TABLE 4.2, Summary of markers of HBV infection. Available from: https://www.ncbi.nlm.nih.gov/books/NBK442290/table/ch4.t2/