Significance of “Anti-HBc Alone” Serologic Status in Clinical Practice

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Summary

Sera identified as positive for total anti-HBc, but negative for both HBsAg and anti-HBs, are referred to as “anti-HBc alone”. This serologic response is compatible with acute, resolved, and chronic hepatitis B virus (HBV) infection but may also signify occult HBV infection. Once the “anti-HBc alone” pattern is detected, false-positive reactivity should be ruled out and further analyses can resolve the clinical status of the donor. The identification of anti-HBc positivity in the absence of HBsAg in organ transplant donors and in candidate patients

for chemo and immunosuppressive therapy requires further investigation due to the risk of hepatitis B virus (HBV) reactivation. False-positive detection, acute infection during the window phase, and resolved or chronic HBV infection are all possible and only distinguishable if the additional assays are performed and measures of liver damage are taken into account. Measurement of serum anti-HBs responses after the administration of HBV vaccination may be useful to distinguish this serological profile. In view of the relatively low risk of HBV reactivation in “anti-HBc alone” patients who are candidates for immunosuppressive treatment, such patients may not require preemptive antiviral therapy, but should be followed on a monthly basis for ALT followed by quantitative HBV DNA testing in those with ALT elevation. According to specific guidelines, nucleoside analogue prophylaxis is recommended in anti-HBc-positive liver allograft recipients and “anti-HBc alone” individuals who receive chemotherapy or biologic therapy and should be continued for 6-12 months after discontinuation of such immunosuppressive therapies to protect against HBV reactivation.

Key Points

1. Anti-HBc is present during different phases of HBV infection. “Anti-HBc alone” serologic status is compatible with acute, resolved, and overt or occult chronic HBV infection.
2. Five possibilities and clinical courses of “anti-HBc alone” are briefly considered: (1) False-positive reactivity; (2) Co-infection with HIV or HCV; (3) Failure to detect HBsAg in anti-HBc positive patients; (4) Different phases during HBV infection; (5) Passive transfer of antibodies.
3. The pattern of anti-HBs response to hepatitis B vaccine and HBV DNA testing may provide additional diagnostic information for interpreting an “anti-HBc alone” result.
4. Anti-HBc-positive organ donors are a potential source of HBV transmission to their recipients in organ transplantation.

5. Reactivation of occult HBV may be triggered by chemotherapy biologic therapies (particularly rituximab) or modulation of patient's immune function.
6. It is strongly advised that all hemato-oncologic patients as well as candidates for organ transplantation or immunosuppressive therapy should be screened for HBV markers and immunized or receive preemptive treatment against HBV when appropriate.

Introduction

Hepatitis B virus (HBV) infection remains an important disease world-wide. It can be either acute or chronic, and can range in severity from being asymptomatic and completely resolving, to severe and symptomatic with progressive, potentially fatal disease (1). HBV has an outer envelope component of hepatitis B surface antigen (HBsAg) and an inner nucleocapsid component of hepatitis B core antigen (HBcAg). HBcAg can be detected in liver, usually in the nucleus, but also in the cytoplasm of hepatocytes but not in serum. Core epitopes of HBV are a potent immunogen. During natural HBV infection, they induce a cellular and humoral immune response manifested in T-cell proliferation as well as production of high anti-HBc titers(2). Hepatitis B "e" antigen (HBeAg) is found as a soluble protein in the blood of HBV carriers and correlates with the degree of viral replication. Anti-HBe antibodies may be detectable regardless of the presence or absence of HBsAg or anti-HBs, but not without anti-HBc. Testing for anti-HBe may offer additional information to that provided by anti-HBc in cases of chronic hepatitis. Thus, of the term "anti-HBc alone" or "isolated anti-HBc positivity" is referred to regardless of the anti-HBe status. Since anti-HBc is present during different phases of HBV infection, testing for anti-HBe may occasionally be indicated only when anti-HBc is positive and HBV DNA is undetectable by a sensitive PCR assay.

Serum HBV DNA, antigen and antibodies associated with this terminology during HBV exposure are shown in Fig.1.

The proportion of individuals with anti-HBc as the only positive HBV serum marker has been reported in different populations ranging between 1-32% (3-6). However, although common, individuals with “anti-HBc alone” who seek medical advice are faced with uncertainty about the clinical significance of this test. This situation arises in diverse clinical risk groups *e.g.* intravenous drug abusers, hepatitis C virus (HCV) and human immunodeficiency virus (HIV) co-infected patients, haemodialysis patients, organ transplant recipients, and pregnant women (7-12).

Search strategy and selection criteria

References for this review were identified through searches of PubMed with the search terms “anti-HBc”, “anti-HBc alone”, “isolated anti-HBc”, “hepatitis B core antigen”, “occult hepatitis B”, “isolated hepatitis B core antibody” and “hepatocellular carcinoma” until February 2016. The search was limited to include only references in the English language.

For the purpose of this review, five possibilities and clinical courses of “anti-HBc alone” are discussed (Fig.2 and 3).

1. False-positive reactivity

Serum HBsAg, anti-HBs, HBeAg, anti-HBe and HBV DNA when relevant, should be assessed in patients at risk. A positive result, and especially detectable circulating HBV DNA, may provide important information with practical implications in patients with overt or occult chronic HBV infection. Although modern immunoassays for anti-HBc are highly specific, washing

errors and instrument failures may occur, and serum samples may have been mixed up or contaminated. This should be excluded by a repeated assay of anti-HBc, and a second serum sample should be requested if an individual has been found to be “anti-HBc alone” for the first time. If anti-HBc is repeatedly positive, but all the other assays are negative, the specificity of the anti-HBc reaction should ideally be checked by an assay from a different manufacturer. Although radioimmunoassay (RIA) has been shown to be more specific for anti-HBc detection than enzyme immunoassay (EIA), RIA is not used anymore in the majority of clinical laboratories which are mainly using EIA technology for this purpose. The presence of anti-HBc in the absence of anti-HBs and HBsAg may thus signify a false-positive result related to method specificity, particularly when testing is performed by EIA (5, 13-18). Parkinson *et al.* compared these two methods and found that most serum samples positive for anti-HBc by EIA, but negative by RIA, have low levels of anti-HBc (19). In a study in which 133 "anti-HBc alone" positive individuals were tested by EIA “re-testing” by RIA, revealed that 26% samples became anti-HBc negative. In addition, circulating HBV DNA was undetectable in 96% of these "anti-HBc alone" positive (by EIA) serum samples (20). Cross-reactivity with interfering serum substances or with immune globulin IgA- or IgM- molecules secreted by non-specific HBV-activated B lymphocytes may be another cause of anti-HBc false-positivity (21-23). Pretreatment of blood samples with reducing agents, *e.g.* dithiothreitol (25^{o}C; +DTT) or potassium bisulfite (37^{o}C; +MBS), can help avoid non-specific false anti-HBc positivity (24, 25). Thus, differences in pretreatment, incubation, and washing protocols may be responsible for false-positive results.

Although there is now a WHO standard for anti-core allowing labs to quantify levels of antibodies, there is no licensed or FDA approved confirmatory assay for anti-HBc. This is unfortunate since even the most recent generation of

assays still generates substantial false positivity. Due to the lack of such a confirmatory assay, re-testing with an alternative assay is a good substitute provided sensitivity is equivalent. Sensitivity can be evaluated against the WHO standard.

The titer of anti-HBc may also be useful in defining the significance of a result. Non-specific results are often weakly positive, occasionally are borderline positive after repetition, and often cannot be reproduced by another test kit. The Japanese Red Cross blood centers have reported that blood donors with low anti-HBc titer (S/CO values between 1.0 and 11.9) may carry low level of HBV DNA, suggesting occult HBV infection (OBI) and such donations were infectious to recipients. As a result, all anti-HBc reactive donors are now rejected (26, 27). A higher anti-HBc titer (S/CO $\geqslant$ 12.0) is more likely to imply past (or present) infection. However, overall, it is unclear what fraction of the total “anti-HBc alone” results reported in patients are false-positive, and how many provide true evidence for past hepatitis B exposure. Table 1 (20, 28-35) shows a summary of the relevant studies with respect to this point.

2. Co-infection with HIV or HCV

Several studies have reported an association between the presence of “anti-HBc alone” and HCV or HIV co-infection (7, 36-40). Thus, viral interference by other viruses in the replication or immune response to HBV could be involved in the phenomenon of “anti-HBc alone”. Putative mechanisms such as down-regulation of HBV gene expression as well as mutations in the HBV genome may modulate the cellular and humoral immune response to HBV.

Many published reports support the observation that the serologic anti-HBc only positivity is a common clinical finding in patients with hepatocellular carcinoma (HCC) infected with HCV (60-63), suggesting potential interference

between HBV and HCV replication (64). Inigo *et al.* revealed that HCV core protein suppresses HBV replication and HBsAg production, thus affecting its detection in the bloodstream of HCV/HBV co-infected patients (64). HCV may suppress not only the replication of HBV, but also the expression of HBV envelope proteins *in vitro* and *in vivo* (65, 66). Furthermore, several studies have shown that HIV-infected individuals may frequently be co-infected with HBV, and anti-HBc is usually the only positive HBV serological marker indicating persistent HBV infection in this group (9, 10). Most recently a study from Switzerland, where the prevalence of HBV infection is low (1), showed 23 of 31 (74.2%) “anti-HBc alone” subjects were co-infected with HCV. In this cohort, infrequent intrahepatic total HBV DNA (2/22, 9.1%) and cccDNA (1/22, 4.5%) tested by nestedPCR were detected in liver biopsies. Our group used recombinant proteins HBsAg (ay), HBsAg (ad), HBV core (1-186 a.a.), and a total number of 49 HBsAg- and HBcAg-derived peptides for analyses, then all anti-HBc positive patients showed an HBV-specific T cell and memory B cell response typical for past viral exposure and protective immune memory, suggesting resolved HBV infection (67). Consequently, in view of the relatively high frequency of HCV and/or HIV co-infection in “anti-HBc alone” patients, HCV and HIV antibodies should be tested in such patients.

3. Failure to detect HBsAg in anti-HBc positive patients

HBsAg may remain negative in blood for up to six months following exposure and infection with HBV, *i.e.,* in blood donors who are within the “immunological window” of a recent infection (55, 68-73). However, excluding recent HBV infection, HBsAg in small amounts, may still be present in patients persistently infected with HBV which are beyond the detection capability of currently used assays. Moreover, presence of HBsAg may be masked by non-neutralizing, circulating anti-HBs molecules (74). Presence of HBV infection in such patients may be verified through detection of HBV DNA by PCR (13, 74).

The finding of anti-HBc without HBsAg in patients with chronic hepatitis with still undetermined etiology is difficult to interpret, as the absence of HBsAg does not invariably exclude an etiological role for HBV. Detection of high titers of anti-HBc may support this assumption. Testing for anti-HBe is sometime advised in such cases.

Moreover, spontaneous or iatrogenic generation of HBsAg mutants may lead to evasion of immune detection of circulating HBsAg by conventional immune-assays. HBV has a higher frequency of mutations than other DNA viruses because the virus replicates via an RNA intermediate, using a reverse transcriptase that lacks a proof-reading function. This may lead to generation of point mutations, deletions, and re-arrangements in the HBV genome which lead to modulations of HBsAg, expression, secretion, and synthesis despite active viral replication. Mutations in the major hydrophilic region (MHR) of S protein may affect the binding of the mutated surface antigen to anti-HBs antibodies detected through routine EIA assays. Thus, such HBsAg mutants escape detection leading to a serological profile of “anti-HBc alone” (41-48). For example, the lack of HBsAg detection may depend on mutations in the “a” determinant, while nucleotide deletion in the core promoter region might also cause lower levels of S gene expression or viral replication (49-58). A frame shift in the S-open reading frames (S-ORF) on one of three clones suggested that there was a counter-selection against production of HBsAg (59). Such mutations may lead to aberrant HBsAg molecules which cannot be detected with licensed screening tests, but can be verified using unconventional EIAs with monoclonal antibodies.

The hepatitis B virus has overlapping ORFs. A potential impact of nucleoside analog therapy on HBV mutations, and concomitant HBV S gene mutations has been shown recently (75, 76). This has been noted in HBV/HIV co-infected individuals treated with anti-HIV therapy, such as Lamivudine(3TC) (77).

It has been clearly indicated that amino-acid substitutions in the MHR affect

HBsAg detection, in particular those substituting cysteines (78, 79). Different tests are able to detect different specific mutations, some are not detected at all (80). Out of the many described mutations for HBsAg, these are the most common described mutations: G145R, P120S, P120T, A128V, and T118A (81, 82). Such mutations may lead to aberrant HbsAg molecules which cannot be detected. As a result, testing anti-HBc only samples with several HBsAg assays might reveal such false negative cases. Not only MHR mutations, mutations in the core gene and frame shifts but also immune complexes masking HBsAg (and anti-HBs) and MHR mutations associated and probably causal of lack of HBsAg excretion are reported by Biswas *et al* (83).

4. Different phases during HBV infection

4.1. Acute window phase: The average incubation period of acute hepatitis B is 90 days (ranging from 60 to 150 days) (84, 85). Total (IgG and IgM) anti-HBc and IgM anti-HBc appear at the onset of clinical symptoms and rapidly reach peak concentrations. An IgM class of anti-HBc is often considered to be a relatively precise marker for the differential diagnosis between acute hepatitis B (persists for up to six months if the disease resolves) and acute exacerbation-reactivation of chronic HBV infection (1). However, it can also be detected at high titers by qualitative assays in exacerbation of chronic hepatitis B (86). On the other hand, the difficulty in obtaining high levels of IgM anti-HBc performance with such a test should be mentioned, particularly regarding specificity. The decrease in IgM anti-HBc titers during convalescence occurs at variable rates while IgG anti-HBc generally persists for life. The highest titers occur in patients with persistent infection (87-90). Once the “anti-HBc alone” profile is confirmed by repeated anti-HBc testing, anti-HBs should be tested after another one-to-three months. Anti-HBs seroconversion will confirm that the initial anti-HBc positivity had been recorded during the “acute window

period", especially when IgM anti-HBc is positive (Fig.1).

4.2.1. Patients with chronic hepatitis B: Presence of HBsAg in serum for at least six months is considered as evidence for persistent HBV infection. In people who become chronically infected, HBsAg and anti-HBc persist, typically for decades and possibly for life with a HBsAg clearance and anti-HBs seroconversion rate ranging between 3-6% (91). (54, 92)Furthermore, HBV DNA may still be detectable in serum of asymptomatic HBsAg carriers as well as in HBsAg negative/anti-HBs/anti-HBc positive individuals with normal liver function. The latter group may in fact remain "latent" chronic HBV carriers with low level of HBV replication, which can "reactivate" during periods of immune suppression (93-95).

The interpretation of the significance of "anti-HBc alone" in a particular patient is directly related to the endemicity and risk of HBV in the population tested. In patients residing in regions where the population has a very low HBV prevalence, such as in most parts of Europe and the U.S., it frequently represents a false-positive reaction. In such a population, a primary conventional anti-HBs response to immunization after a one to three-dose series of hepatitis B vaccine can confirm the diagnosis of a false positive anti-HBc reaction. In contrast, in highly endemic countries, *i.e.* in South East Asia, most of the Middle East, the Amazon Basin, most Pacific Island groups, and the sub-Sahara, HBV is mainly acquired during the perinatal or early childhood period. Therefore, "anti-HBc alone" most likely indicates previous infection, with loss of anti-HBs. (1, 5, 96-98). (99)

4.2.2. Occult HBV infection (OBI): OBI is defined as low plasma levels of HBV DNA with undetectable HBsAg outside the pre-seroconversion window period (1). A large number of studies on OBI focused on "anti-HBc alone" although many following studies demonstrated that OBI can occur in anti-HBs positive and even vaccinated individuals (30, 64, 100-103). In many studies conducted e.g. in blood donors, "anti-HBc alone" represents approximately 40% of OBIs

(26,27). Therefore, any “anti-HBc alone” sample should be tested with highly sensitive HBV DNA assay - the median load is 20-25 IU/ml. Immunization with one dose of an HBV vaccine may also enable a distinction between latent and OBI groups (99). An anmnestic anti-HBs response to one HBV vaccine dose will confirm the presence of an immune memory to HBV with resolved HBV infection while absence of such a response and/or detection of HBV DNA in serum will confirm the diagnosis of occult HBV (see next paragraph). In patients with persistence of HBV DNA synthesis, this may be associated with liver injury and progression to cirrhosis and HCC (1). One analysis of occult HBV isolated from patients with hepatocellular carcinoma showed that multiple viral variants accumulated in the liver of these patients, suggesting that host, rather than viral factors were responsible for cryptic HBV infection (54). Kwak *et al*. reported that 84.6% of patients with cryptogenic HCC (cHCC) had anti-HBc IgG antibodies in Korea, but this subgroup had different clinical features to those of HBV HCC patients, suggesting that the presence of anti-HBc might modify the characteristics of HCC towards those of HBV HCC (92).

4.3. Resolved phase: Not all unusual patterns of serological reaction to HBV are due to genetic viral variants. HBsAg may be undetectable in serum due to masking by circulating anti-HBs. By convention, disappearance of HBsAg and seroconversion to anti-HBs antibodies following acute infection, indicates the resolution of HBV infection. During the initial period following acute infection, anti-HBc may be present during the “window” phase when HBsAg has disappeared and anti-HBs has not yet appeared, usually within three-to-four months (104). In this context, it should be remembered that commercially available assays are not adjusted to detect very low anti-HBs levels beyond 10 mIU/ml, leading to “anti-HBc alone” serostatus (105-107). During this early phase of infection, anti-HBs antibodies may also bind to their corresponding

antigens, forming HBsAg-anti-HBs immune complexes (107); Finally, this condition could also be due to the decay and loss of immune memory decades after primary HBV infection and especially in countries where repeated exposure to HBV infected individuals with high viral load will lead to breakthrough of the immune memory. Despite undetectable serum anti-HBs, the HBsAg-specific T cell immune response plays an important role in protecting HBV infection and replication (108). Because of this cellular immune memory and mechanism, “anti-HBc alone” individuals seem to have a signature of late immunity and be protected against re-infection. HBV-resolved individuals with undetectable levels of anti-HBs antibodies will develop a strong secondary immune response after the hepatitis B vaccine (109).

It is noteworthy that anti-HBc can also indicate resolution of long-term chronic infection (*i.e.*, not just resolution of recent/acute infection). It is estimated that ~1-2% of chronic hepatitis B carriers (especially long-term inactive CHB carriers) can spontaneously lose HBsAg with or without presence of anti-HBs antibodies (1, 110).

5. Passive transfer of antibodies

Anti-HBc can be passively acquired through transfusion with anti-HBc-positive blood. Infants born to HBsAg-positive mothers and who do not become infected may have detectable anti-HBc for up to 24 months post-partum as a result of passively transferred maternal anti-HBc antibody. Furthermore, intravenous immunoglobulin (IVIG) which is a plasma-derived product consisting of concentrated immunoglobulin may contain anti-HBc antibodies which may passively be transferred to recipients. A retrospective study found an odds ratio of 16 (95% CI: 1.5-166.1) for anti-HBc positive participants who had IVIG infusions in the past (111). The antibodies passively acquired through administration of IVIG have an estimated 21- to 24-day half-life and are usually cleared from the circulation (112). Thus, patients with anti-HBc

alone should be interviewed regarding to recent treatment with IVIG or blood product transfusion and retested for anti-HBc within 3-6 months of presumed exposure.

(83)

The role of HBV vaccination in clarifying the significance of isolated anti-HBc antibodies

Hepatitis B vaccines are formulated to contain 3 to 40 µg of HBsAg protein per milliliter and an aluminum phosphate or aluminum hydroxide adjuvant. The pattern of anti-HBs response to hepatitis B vaccine may provide additional diagnostic information for interpreting an “anti-HBc alone” result. Primary response and seroprotection against HBV is defined as ≥10 mIU/mL of anti-HBs one month after a standard three-dose vaccination regime (zero, one, and six months) (113). Most healthy children and adult vaccinees will develop much higher anti-HBs levels than 10 mIU/ml, ranging between hundreds to thousands mIU/ml following three doses of HBV vaccine (98). Non response to vaccination is defined as anti-HBs < 10 mIU/mL after the third dose of vaccination (114). An anamnestic response was defined as a switch of anti-HBs from < 10 mIU/mL to ≥ 10 mIU/mL two-to-three weeks after administration of one booster vaccine dose (20, 115, 116). Those anamnestic response subjects for which the serum anti-HBs level was ≥ 10 mIU/mL but < 100 mIU/mL were deemed to be demonstrated a borderline protective status, even more, ≥ 100 mIU/mL was suggested a protective anti-HBs status (117).

In cases which develop a primary response to 3 doses of the vaccine, an “anti-HBc alone” positivity is presumably false-positive (35). No response to vaccination suggests occult HBV infection (which should be confirmed by HBV DNA testing), while an anamnestic response is consistent with past infection

and immunity (20). It should be noted that OBI with anti-HBc alone can occur in vaccinated individuals with low anti-HBs or no detectable anti-HBs. This is associated with contact with high viral load HBV of a genotype other than A1 (the vaccine's genotype) as reported by Stramer *et al* (118). Several studies have evaluated the anti-HBs response to immunization with an HBV vaccine in “anti-HBc alone” subjects (20, 67, 101, 116). A rapid and robust response to a booster vaccine suggests a long-lasting anamnestic response (119). Similarly, in a study from Taiwan, among 46 children who were vaccinated against HBV at birth, 2 (4.3%) were “anti-HBc alone” at age distribution of 6-8.9 years old (101). Recently, one study has reported that anti-HBs levels decrease in a healthcare workers population who vaccinated as adults 10 to 31 years post-vaccination and fall below a level considered protective in 25% of cases (119). From our group’s data, two-to-three weeks after the administration of one dose of HBV vaccination, in two of six (33.3%) “anti-HBc alone” cases, anti-HBs antibody levels in plasma became greater than the protective cut-off level (10 and 12 mUI/ml, respectively). However, this was accompanied by an expansion of HBsAg-specific memory B cells, which were significantly stronger in the B cell ELISpot than before vaccine (P = 0.0226) (67). This has demonstrated that immune memory against HBV infection lasts longer than anti-HBs antibodies. Table 2 describes an anamnestic response in “anti-HBc alone” individuals as well as in those immunized about twenty years ago (30, 67, 109, 117, 120, 121).

Of note, anti-HBs tends to become undetectable relatively early, so “anti-HBc alone” is typically a recovered infection with undetectable anti-HBs. On the other hand, HBsAg tends to decline over a much longer period of time but may become undetectable, leaving anti-HBc as the only marker of chronic infection. In both situations, sensitive detection of HBV DNA is critical to diagnosis.

The significance and clinical implications of "anti-HBc alone" in immune-suppressed patients receiving chemo or immunosuppressive therapy and in organ donors

Hepatitis B virus reactivation is a serious, often life threatening complication which affects a number of risk groups including patients given chemo and immunosuppressive therapy as well as organ transplant recipients. By now, there is a worldwide consensus that HBsAg-positive patients should be protected against HBV reactivation when receiving immuno-suppressive therapy (1). Reactivation can occur in patients who are HBsAg-positive/anti-HBc-positive or HBsAg-negative/anti-HBc-positive (122). Unfortunately, antiviral prophylaxis was infrequently administered to cancer patients receiving chemotherapy. A recent survey conducted by the members of the American Association for the Study of Liver Diseases (AASLD) who were primarily hepatologists and gastroenterologists reported that the overall frequency of prechemotherapy HBV screening was only 53% in a cancer patients cohort. Moreover, 23% of the HBV-reactivated patients died of liver failure (123). However, there still is a debate regarding the means for protection of anti-HBc-positive patients having cancer chemotherapy or organ recipients from "anti-HBc alone" donors. Some studies have shown the benefit of antiviral prophylaxis in HBsAg-negative/anti-HBc-positive patients with lymphoma patients or undergoing hematopoietic stem cell transplantation (124, 125). All in all, it appears that "anti-HBc alone" as well as anti-HBc-positive/anti-HBs-positive patients are also at risk for HBV reactivation under conditions of immune suppression although this risk is lower as compared to HBsAg-positive/anti-HBc-positive subjects.

Organ donor shortage has led to an expanded use of grafts from "anti-HBc-positive only" or anti-HBc-positive/anti-HBs-positive donors with past exposure to hepatitis B, especially in areas where the prevalence of the

hepatitis B virus is high (126-128). If possible, anti-HBc-positive grafts should first be transplanted in recipients who have HBV-related liver disease, second to those with antibodies to HBV, and last to HBV naive recipients. Recipients who are anti-HBc-positive are not absolutely protected and should be given prophylaxis, as well. The mandatory use of immunosuppression in organ transplant recipients favors reactivation of latent virus. The vast majority of acquired HBV infections after liver transplantation are related to the donor liver (128, 129). Anti-HBc-positive organ donors have been implicated as a potential source of HBV transmission in 25%-95% of their recipients of orthotopic liver transplantations (OLT); whereas, the risk of *de novo* infection in “anti-HBc alone” positive recipients who have not received prophylactic therapy after OLT ranges from 0%-18% (129-138). In addition, HBV reactivation may also occur in other solid-organ transplantation including renal, heart, lung (128).

Another risk group for HBV reactivation includes "anti-HBc-positive alone" hemato-oncologic patients as well as patients with rheumatic diseases. Several studies highlighted the reactivating risk in anti-HBc-positive carriers who were patients with non-Hodgkin’s lymphoma, chronic lymphocytic leukemia, or rheumatoid arthritis given rituximab (RTX)-based therapy (139). Lee *et al*. reported that HBV reactivation was found in 1.7% (8/468) HBsAg-negative/anti-HBc-positive patients with rheumatic diseases treated with anti-tumour necrosis factor (TNF) agents (100). No definite HBV reactivations were found in anti-HBc-positive patients lacking HBsAg in an inflammatory bowel disease (IBD) cohort treated with immunosuppressants (140).

Reactivation of HBV may be triggered by chemotherapy, biologic therapies (particularly rituximab), or a modification in patient’s immune function (141-150). At present, the most reliable test used in clinical practice to

diagnose HBV reactivation is the demonstration of a rise of one log in serum HBV DNA levels. When HBV reactivation is diagnosed, it is suggested to start antiviral agents immediately (151, 152) (Table 3). It is still debated whether it is "mandatory" to treat all cases that have a one log HBV DNA increase without ALT rise and without HBsAg reappearance. Thus, it could be argued that cases with low-level HBV DNA increase (*i.e.* from undetectable to 1 or 2 log by sensitive PCR assay) could still be fine to continue monitoring.

In HBsAg-negative/anti-HBc-positive patients who are receiving systemic chemotherapies or biologic therapies that modified their immune function, the risk of hepatitis B reactivation is 1%-2.7% (153). Effective prophylaxis against HBV reactivation should be used in this kind of situation. Related strategies for prophylaxis should be implemented in such recipients to reduce or eliminate the risk of developing post-transplant *de novo* hepatitis B infection from anti-HBc positive donors (154). These include passive immunoprophylaxis with hepatitis B immune globulin (HBIG) and drug prophylaxis with the nucleoside analogs (*i.e.* lamivudine, tenofovir and entecavir), separately or in combination. Prophylaxis against reactivation may not require more potent and costly nucleoside analogs (*i.e.* entecavir and tenofovir). Lamivudine may be more cost-effective, especially in anti-HBc positive and HBsAg negative individuals with low-level viremia. The risk of antiviral resistance and virological breakthrough is significantly lower in individuals with low level HBV DNA. However, it should be noted that resistance to lamivudine emerges at high rates (30-50% cases within a year), in contrast to tenofovir (1, 110). HBIG alone does not seem to be absolutely effective in preventing transmission of HBV, while nucleoside analog either alone or in combination with HBIG is effective (1, 98, 136, 154-159). Although anti-HBs and nucleoside analogs have different mechanisms to provide protection that may complement each other, a systematic review has concluded that published studies have not shown HBIG + lamivudine combination therapy to be more effective than

lamivudine treatment alone; furthermore, the latter is more practical and affordable. Nucleoside analogue monotherapy should therefore be considered in preventing HBV infection in HBsAg and HBV DNA negative recipients of anti-HBc positive donor grafts (160). Since HBIG administration is an expensive and inconvenient preventive measure to acquire anti-HBs after liver transplantation, active immunization for recipients, such as pre-transplant HBV vaccination, can be used. Successful active immunization before transplantation and lamivudine after transplant may be sufficient to prevent *de novo* hepatitis B (161). On the other hand, one literature review including 39 studies with 903 recipients of anti-HBc positive liver grafts showed both anti-HBc and anti-HBs positive recipients may need no prophylaxis at all (162), respectively.

Authors' contributions

QW did the literature research, performed the figures together with NS and the writing of the manuscript. PK did the writing and editing of the manuscript. NS did the writing and editing of manuscript, created the figures and tables together with QW.

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Conflict of interest

The authors (QW, PK and NS) declared no conflicts of interest.

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Table 1. Summary of the “anti-HBc alone” studies with false-positive vs. true-positive results.

Study	“anti-HBc alone” (%)	False “anti-HBc alone” positive	Past HBV exposure
Lok AS *et al*.(28)	11.9% (214/1801)	56% (primary response)	16% (anamnestic or secondary anti-HBs response)
Chan CY *et al.*(29)	No information	42% (37/88)	75.5% (37/49 subjects were positive for anti-HBe and/or HBV DNA)
Su FH *et al.*(30)	1.2% (21/1734)	38% (8/21)	61.9% (13/21 anamnestic response, none had evidence of HBV DNA)
Lu SN *et al.*(31)	1.2% (18/1454)	5.6% (1/18)	77.8% (14/18, 12 anti-HBc alone subjects developed an anamnestic, anti-HBs response, two were positive for HBV DNA)
Ural O *et al.*(32)	No information	47.9% (23/48 primary response)	41.6% (20/48 anamnestic response)
McIntyre A *et al*.(33)	No information	41.2% (7/17)	35.3% (6/17 anamnestic response)
Silva AE *et al*.(20)	No information	80.5% (66/82 primary response)	19.2% (25/130 anamnestic response) 3.8% (5/133 HBV DNA positive)
Lai CL *et al*.(34)	8.0% (51/638)	72.9% (35/48 primary response)	4.2% (2/48 anamnestic response)
Sünbül M *et al*.(35)	No information	27.3% (9/33 primary response)	48.4% (16/33 anamnestic response)

Table 2. Anamnestic responses in “anti-HBc alone” individuals and HBV naïve* individuals.

Study	Group	Serum anti-HBs levels after a booster vaccination (mIU/mL)		
		< 10	10 to < 100	⩾ 100
Su FH *et al*.(117)	“Anti-HBc alone”: 1.7% (14/843)	No information	No information	No information
	HBV naïve*: 62.3% (525/843)	24.7% (78/316)	23.4% (74/316)	51.9% (164/316)
Hudu SA *et al*.(120)	“Anti-HBc alone”: 5.0%	0	100%	
Su FH *et al*.(30)	“Anti-HBc alone”: 0.7% (13/1734)	7.7% (1/13)	61.5% (8/13)	30.8% (4/13)
	HBV naïve*: 58.2% (1010/1734)	There was no significant difference in anamnestic response to the vaccine booster dose between true “anti-HBc alone” (50.6 mIU/mL)[#] and “HBV naïve” subjects (47.7 mIU/mL)[#] (*P*=0.90)		
Wang *et al*. (67)	“Anti-HBc alone”: *n*=31	66.7% (4/6)	33.3% (2/6)	0 (0/6)
Gessoni G *et al*. (109)	“Anti-HBc alone”: 0.8% (31/3992)	66.7% (14/21)	28.6% (6/21)	4.8% (1/21)
Bagheri-Jamebozorgi M *et al*.(121)	HBV naïve*: 63.0% (189/300)	138 HBV naïve subjects received a booster dose, 90.6% (125/138) anamnestic response		

*HBV naïve: subjects with full HBV vaccination in infancy and with the status of HBsAg negativity, anti-HBc negativity and anti-HBs negativity in adulthood
[#]The geometric mean titer (GMT) of serum anti-HBs antibodies

Table 3. Clinical approach in the risk of HBV reactivation.

Risk of HBV reactivation	Approach	Goals of treatment
High: HBsAg-positive patients, including both detectable and undetectable HBV DNA	Treated with oral antiviral agents (*e.g.* Entecavir/Tenofovir) 1-2 weeks before and no later than on the first day of immunosuppression therapy. Antiviral therapy should continue at least 6 to 12 months after completion of chemo- or immunotherapy.Prolonged antiviral treatment for an undefined period and possibly lifelong should be considered in patients with advanced liver disease or with baseline high viral load.	Normalization of ALT, suppression of HBV viral load to undetectable levels, and HBeAg seroconversion to anti-HBe. In anti-HBe-positive patients, ALT normalization and viral-load suppression are the main goals of treatment
Low: Occult HBV infection (HBsAg-negative/anti-HBc-positive with or without anti-HBs and undetectable HBV DNA)	Not universally accepted. In case of HBV reactivation, as assessed by significant increase in HBV DNA levels, they should be promptly treated with antiviral drugs, possibly before ALT elevation. Oral antiviral agents (*e.g.* Lamivudine)	

Figure Legends:

Figure 1: Serum HBV DNA, antigen and antibodies responses during HBV exposure in acute, resolved (1A) and chronic (1B) forms

Figure 2: Flow chart: Algorithmic approach for “anti-HBc alone” under different clinical courses

Figure 3: Possibilities and clinical courses of “anti-HBc alone”

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