Isolated anti-HBc: reflections from clinical microbiology and infectious diseases

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Introduction

Anti-hepatitis B core antibodies (anti-HBc) represent important serological markers to identify patients who have been exposed to hepatitis B virus (HBV). The presence of isolated anti-HBc (IAHBc) is not rare, being found in up to 10-20% of the population in endemic countries, i.e., China and Korea, and in 0.4-1.7% of blood donors in low-prevalence areas i.e., Europe and the United States of America.[1] IAHBc tends to be more common in males and increases with age.[2] The prevalence rises in individuals with human immunodeficiency virus (HIV) and hepatitis C virus (HCV) coinfection. IAHBc is a particular serological pattern, defined by negative HBV surface antigen (HbsAg) and negative HBV surface antibody (anti-HBs). Although IAHBc can be due to false-positive reactivity, this pattern can be found either during the serologic window of acute hepatitis, or many years following the resolution of HBV infection, owing to a decrease to undetectable titres of anti-HBs, or, seldomly, after many years of chronic HBV infection, when HBsAg decreases to titres below the limit of detection. Although microbiological flow charts and clinical guidelines exist, a controversy persists regarding the management of patients with IAHBc who are under risk of HBV reactivation and of healthy blood donors. Herein, we discuss microbiological and clinical management of cases with IAHBc.

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Management of IAHBc at the Clinical Microbiology Laboratory

Because of presumed lower specificity of automated assays, cases with IAHBc should be evaluated carefully. To rule out false positivity, the analysis should be repeated after centrifugation. If the same result is obtained, it is recommended to re-test for the IAHBc pattern with another assay. For cases with confirmed IAHBc, we recommend complementary analysis with anti-hepatitis B e antibody (anti-HBe), HIV-screening and HCV-screening. To evaluate for occult HBV infection, HBV-DNA quantification in blood should also be measured.

Clinical management of IAHBc in different risk groups

a. Immunocompromised patients

Hepatitis B reactivation risk in patients with IAHBc should be stratified according to type of immunosuppressant drug and underlying disease into high-, moderate- and low- risk groups.[3,4] The risk of reactivation is >10% in the high-risk group, 1-10% in the moderate risk group and <1% in the low-risk group. Bone marrow/solid organ transplantation, rituximab and other B-

cell agents are associated with high reactivation risk. Moderate/high doses of corticosteroids (prednisolone ≥10 mg/day for >4 weeks), tissue necrosis factor-alpha inhibitors, systemic chemotherapy are related to moderate risk, while lower doses of corticosteroids, methotrexate and azathioprine are associated with low risk.

In terms of therapeutic management, two options have been proposed. First, preemptive therapy can be considered, with repeated HBV-DNA monitoring, starting the antiviral drug at a specified HBV-DNA level.[5] This is a reasonable strategy, but the optimal interval and time span of monitoring are not clearly defined.[6] The other strategy is to prescribe antivirals for HBV prophylaxis, at the time of starting the immunosuppression. This strategy aims to prevent the reactivation of HBV and avoid the cost of serial HBV-DNA assessments. Indications for treatment differ between the three categories. Antiviral prophylaxis is recommended for the high-risk group. It is also recommended for the moderate-risk group (although there is no consensus on this). Antivirals are not recommended for the low-risk group who require monitoring and a treatment-on-demand strategy, instead.[4]

b. HIV- and HCV-coinfected patients

As previously mentioned, IAHBc is frequent in people living with HIV. However, the risk of reactivation of HBV infection in these patients is low.[7] For this reason, American and European HIV guidelines do not give any specific recommendation on the type of antiretroviral regimen to be administered in these patients.[8] Specifically, guidelines do not recommend including an anti-HBV agent in the antiretroviral regimen.

Beyond treatment, HBV vaccination could be helpful in preventing HBV reactivation. It has been shown that an anamnestic response to a single dose of HBV vaccine ranges between 7-32% in HIV infected patients with IAHBc. A recent meta-analysis showed that the full series of double dose of the HBV vaccine is associated with better immune responses than the standard HBV vaccine regimen for HIV infected patients.[8] Therefore, in some countries, it is recommended for HIV-coinfected patients with IAHBc to get a single standard dose of HBV vaccine and evaluate their immune status. If their anti-HBs is <100 IU/mL, then they must get the full series of either single or double-dose HBV vaccine.[9]

In people living with HCV, HBV reactivation has been reported during treatment with direct-acting-antivirals (DAAs), as a result of the virological reciprocal inhibition.[10] In case of IAHBc, the estimated risk is below 1%.[11] Given the low risk, prophylaxis is not recommended. HBV reactivation should be suspected in case of an unexplained increase in liver aminotransferase levels during and/or after completion of DAAs therapy.[4]

c. Patients undergoing transfusion or transplantation

Transmission of HBV infection can occur from IAHBc donors.[12] This risk is greater where anti-HBs is negative. The problem of transfusion-related HBV transmission from IAHBc donors is complicated and may be underestimated because of multiple potential reasons, such as: HBV-DNA may be undetectable or intermittently detectable in IAHBc donors, tracing recipients is resource-intensive, and the low incidence of clinical disease in recipients may therefore go unnoticed. Anti-HBc testing for donors has been implemented in some countries to improve blood safety. This strategy compensates for the lack of sensitivity of nucleic acid (NAT) testing.[13] The main problem with anti-HBc testing is that it can result in the unnecessary deferral of a high number of donors. Further work is needed to identify those most at risk of onward transmission to reduce unnecessary deferral, in particular of those with rare blood types.

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