

## Clinical Practice Guidance for Management of Anti HBc Positive Patients

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### Summary:

*Hepatitis B core antibody (Anti HBc) is currently considered the most sensitive serological marker for a patient's history of hepatitis B virus (HBV) infection given its long-term persistence in the bloodstream. The serological pattern of isolated Anti HBc (IAHBc) has been of clinical interest over the past several years. The growing data of IAHBc suggesting it as a marker for occult HBV infection (OBI). Occult HBV infection defined as HBV DNA detection in serum or the liver by sensitive diagnostic tests in HBsAg negative individuals with or without serologic markers of previous viral exposure. OBI is especially concerned in blood transfusion (BT), organ donation and reactivation of HBV infection following immunosuppressive therapy. HBV reactivation depends on viral and host factors. The important clinical implications of IAHBc is in the setting of co-infection with hepatitis C virus (HCV), reactivation risk of HBV during*

*directly acting anti viral (DAA) therapy in HCV infection which may lead to progression of liver disease and hepatocellular carcinoma (HCC). Antiviral prophylaxis has been recommended in moderate to high risk of reactivation prior to immunosuppressive and biologics. The main goal of therapy is to improve survival and quality of life by preventing disease progression and to prevent consequent development of HCC. It is proposed to perform Anti-HBc test as a screening test prior to blood transfusion, HBV vaccination, DAA and immunosuppressive therapy in addition to HBsAg screening test.*

*Keywords: Hepatitis B Virus; Hepatitis B virus DNA; Occult hepatitis B virus infection; Hepatocellular carcinoma; Hepatitis B surface antigen,; Anti HBc total; Bangladesh*

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### Introduction:

Hepatitis B Virus (HBV) is a major global public health concern. Over 2 billion people worldwide had been

infected and 250 million people in world are chronically infected with HBV<sup>1</sup>. Regional prevalence of HBV is highest in sub Saharan Africa and South East Asia between 5-10%<sup>1</sup>. Bangladesh belongs to an intermediate prevalent region, which is about 4.2%<sup>2</sup>. Another study conducted at Savar, a suburban area of Bangladesh revealed prevalence of HBsAg is 5.5%<sup>3</sup>. Hepatitis B core antibody (Anti HBc) is one of the most important serological markers of HBV infection. In HBV endemic area prevalence of Anti HBc is high. In Bangladesh prevalence of Anti HBc among general population is 31%<sup>2</sup>, among chronic kidney disease patient is 39.3%<sup>4</sup>. Another study conducted in Kallyanpur, a densely populated community in Dhaka, Bangladesh explored its prevalence is 47.7% among 384 healthy subjects<sup>5</sup>. General populations as well as physicians are very much worried about Anti HBc positivity. In special situation like co-infection of HCV and HBV, immunosuppression, blood transfusion, organ donation. No local guide line exists from any professional. So a local guidance for management recommendation is needed for proper handling of Anti HBc positive cases.

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**Methodology:**

We have explored all the online publications available on HBV of Bangladesh from beginning to 2018. We have reviewed the guide lines and recommendations published on HBV and or Anti HBc by professional bodies of Asia Pacific region, European association and United states from 2010 to 2018. Here anti HBc and Anti HBc total considered as clinically synonymous.

**Discussion:**

Anti HBc as a serological marker

AntiHBc is recognized as an important serological marker for hepatitis B virus infection identifying patients infected with hepatitis B virus infection and persists for life. Regardless of whether the HBV resolves or remains chronic. AntiHBc is found in different phases of HBV infection: acute, chronic, resolved HBV infection, occult HBV infection (OBI), as well as false positive cases. Anti HBc positive with HBsAg positive indicates ongoing infection. High degree of suspicion with persistently raised transaminases and or chronic liver disease where other causes were excluded would direct for further evaluation. Occult, HBV infection, where low viraemia is detected by HBV DNA in serum or liver. Very rarely hepatitis B virus core (HBc) antigen may persist in the nucleus of hepatocyte. Immunosuppression may cause reactivation (reappearance) of HBV infection.

Spectrum of clinical conditions with Isolated Anti HBc (IAHBc)

Current literature has used the IAHBc specifically to HBsAg-negative, antiHBc-positive patients, often stratifying this population into antiHBs-positive and Anti HBs-negative subgroup<sup>6</sup>. IAHBc can occur for variety of phases.

- a. Previous exposure to HBV: It is the most common reason for Anti HBc positivity. These persons recovered from acute HBV in past and Anti HBs has waned to undetectable level, but some had been chronically infected with HBV for decades (with DNA 20 -200 IU/ml) before clearing HBsAg. They are still in minor risk of developing HCC like inactive chronic HBV with undetectable DNA<sup>7,8</sup>. If IAHBc is confirmed, consideration of subsequent testing should be pursued to evaluate for OBI<sup>9</sup>.
- b. False positive: less commonly antiHBc may be a false-positive test result, particularly in

low prevalence areas<sup>10</sup>.

- c. Window phase: AntiHBc may be the only marker of HBV infection during the window phase of acute hepatitis B; these persons should be tested for anti HBc immunoglobulin M.
- d. False Negative HBsAg: In case of HBsAg mutations that leads to false-negative HBsAg with ongoing HBV infection<sup>11</sup>. In this rare condition Anti HBc will be positive and HBsAg will be negative.

**Occult HBV infection (OBI)**

OBI refers to the presence of HBV DNA in the absence of detectable hepatitis B surface antigen<sup>12</sup>. OBI can be defined by the presence HBV DNA in the serum or liver tissue with either seropositive or seronegative status<sup>13</sup>. High risk group for OBI: Blood donors, transplant recipients, patients co-infected with HCV, HIV immunosuppressive therapy or hemodialysis, cryptogenic liver disease, intravenous drug abuser and healthcare workers<sup>15</sup>.

**Types of OBI**

Seropositive OBI: Seropositive OBI is characterized by detection of anti HBc with or without Anti HBs antibody with detectable HBV DNA<sup>12</sup>.

Seronegative OBI: Seronegative OBI is described by undetectable both Anti HBc and Anti HBs with detectable HBV DNA<sup>12</sup>.

Most OBI is seropositive but around 20% of OBI are seronegative representing a population negative for all serum markers of HBV infection but detectable HBV DNA<sup>14</sup>.

Prevalence: OBI varies worldwide. Prevalence rates of OBI are influenced by several factors as follows: (1) geographic differences (endemicity); (2) Co morbid diseases such as chronic hepatitis C; and (3) and the different diagnostic techniques<sup>15</sup>. OBI was reported higher in HBV endemic area, where 41-90% people had previous exposure to HBV<sup>16</sup>.

If IAHBc is confirmed, consideration of subsequent testing should be pursued to evaluate for OBI. Kanget al.<sup>17</sup> described rates of occult infection ranging from 0% to 22.5%. They also provided an updated range of 1.7% to 41%, reporting on subjects who are HBsAg negative, anti-HBc positive, and HBV DNA positive among a sample of studies from 2001 to 2015 around the

globe. OBI is primarily been associated with the suppression of viral replication and gene expression. However, it has also been seen in patients with mutant forms of HBV with undetectable HBsAg. OBI is significant in various clinical contexts including viral transmission with blood transfusion and organ donation, reactivation after biologics, chemotherapy, and antiviral and progression of liver disease including HCC.

IAHBc total positivity with or without HBV DNA positive around the world is 7.7% in Germany<sup>18</sup>, 3.7% in USA<sup>19</sup>, 4% in UK<sup>20</sup>, 8.2% in Mexico<sup>21</sup>, 22.8% in India<sup>22</sup>, 3 % in Australia<sup>23</sup>, 1.7% in Korea<sup>17</sup>, 30 % in Iran<sup>24</sup>, 18.5 % in Egypt<sup>25</sup> and 16 % in Laos<sup>26</sup>.

#### Indication of screening HBV DNA

IAHBc cases with regard to the consequence of OBI, for improving the treatment and management, the screening of HBV DNA by real-time PCR should be implemented in the following groups: (1) patients with a previous history of chronic HBV infection; (2) Co infection with HCV or HIV; (3) patients undergoing chemotherapy with anti-CD20 therapy; (4) any recipients of organ transplantation; (5) organ transplant donors; (6) thalassemia or hemophilia patients; (7) health care workers; (8) patients with cryptogenic hepatitis or cryptogenic liver related disease: cirrhosis and HCC and (9) haemodialysis patients<sup>13</sup>.

#### IAHBc with HCV Co Infection

Chronic HBV infection along with HCV co infection accelerates liver diseases progression and HCC. Treatment with DAAs may cause reactivation of HBV. Patients with HBsAg negative AntiHBc positive are at very low risk of reactivation with HCV DAA therapy<sup>27</sup>. For Anti HBc positive, HBsAg negative patient monitoring of ALT is reasonable, HBsAg and HBV DNA is recommended if ALT fail to normalize or increase despite declining or undetectable HCV RNA level<sup>27</sup>. Joint American Association for the Study of Liver Diseases and Infectious Diseases Society of America guidelines recommend all patients undergoing HCV DAA therapy be evaluated for HBV co infection by measuring HBsAg, antiHBs, and antiHBc<sup>28</sup>.

#### Immunosuppressed conditions

HBV reactivation is a key consideration when initiating immunosuppressive therapy. The 2015 American

Gastroenterological Association guidelines summarized the prevention and treatment of HBV reactivation during immunosuppressive therapy<sup>29</sup>. When considering IAHBc positive patients, the use of antiviral prophylaxis/preemptive therapy is categorized by level of risk of reactivation, with types of immunosuppression categorized into low, moderate and high risk groups depending on perceived intensity of therapy and associated risk<sup>12</sup>.

**Low risk:** Isolated Anti HBc positive patient treated with Azathioprine, 6 mercaptopurine, MTX, Intraarticular steroid, Oral corticosteroid < 1 week of any dose.

**Moderate risk:** Isolated Anti HBc positive patient treated with TNF Alfa I (Infliximab, etanercept, adalimumab, cerolizumab), Cytokine and Integrin inhibitor (abatacept, ustekinumab, natalizumab), tyrosine kinase inhibitor (imatinib, nilotinib), prednisolone <10mg >4 weeks and with Anthracycline with HBsAg Negative (Doxorubicin)

**High Risk:** Isolated Anti HBc positive patient with B cell depleting agent (Rituximab, Ofatumumab), Anthracycline with HBsAg positive (Doxorubicin, Epirubicin) and with patient treated with 10-20mg Prednisolone >4 weeks.

#### HCC risk with IAHBc:

A meta-analysis was conducted on 10 observational studies in 2010 evaluate role of anti-HBc positivity for the risk of HCC in HBsAg-negative subjects with chronic liver disease<sup>30</sup>. Serum antiHBc, an indirect serological marker of occult HBV infection and may be associated with HCC. Study demonstrates that occult HBV patients have a significantly higher risk of HCC than the antiHBs/antiHBc negative. IAHBc was found to have a significantly higher risk of HCC than with antiHBs positive.

Here it may also be hypothesized that circulating antiHBs may prevent the risk of HCC, most probably by controlling HBV replication. Meta-analysis indicates that, at least for HBsAg-negative/antiHBc-positive patients with chronic liver disease, a more accurate monitoring for HCC is hypothesized. This is evident for both Asian and non-Asian populations, in different stages of chronic hepatitis, in HCV etiology, and in patients with or without circulating anti-HBs. The risk of HCC seems to be lower in anti-HBs/anti-HBc-positive patients than in those with "isolated" anti-HBc,

suggesting some inhibitory effect of anti-HBs on occult HBV replication.<sup>30</sup>

### Blood transfusion

Unsafe blood transfusion is one of the routes of transmission for HBV infection. Despite, all blood donations being tested routinely for HBsAg as a marker of transmissible HBV. HBV is transmitted by blood transfusion more frequently than HCV & HIV. In low prevalent area such as Europe and North America, < 5% of blood donors are characterized as having occult hepatitis B. On the contrary, occult HBV may be the major cause of transfusion transmitted HBV infection in high prevalence areas. Iranian study demonstrates HBV infection among anti HBc positive donor in range between 11.3% and 28.6 %<sup>31</sup>. FDA recommends testing of HBsAg and Anti HBc for blood transfusion and organ donation<sup>32</sup>.

### Non liver solid organ transplant recipients

All patients of non liver solid organ transplantation should be tested for HBsAg, antiHBc, & antiHBs. HBsAg positive non liver transplant recipient have a higher mortality rate with liver related complication. All HBsAg positive organ transplant recipients should receive

lifelong antiviral therapy tenofovir alafenamide, tenofovir disoproxil fumarate or entecavir. HBsAg negative antiHBc positive non liver transplant recipients should be monitored for reactivation, alternatively antiviral therapy for the first 6-12 months. The period of maximum immunosuppressant, may be considered<sup>27</sup>. Monitoring should be with ALT 3 monthly & by HBV DNA if ALT rise<sup>33</sup>.

Vaccination of HBV in Anti HBc positive person: Clinicians should screen HBsAg, Anti HBc, and Anti HBs for HBV in high-risk persons, including persons born in countries with 2% or higher HBV prevalence (Table I). Low prevalent countries recommend HBV vaccination in presence of Anti HBc in absence Anti HBs and HBsAg. All Asian countries including Bangladesh have > 2% HBV prevalence<sup>27</sup>.

### 4. Guidance:

As per present status of information and evidence to generate guide line is not sufficient for the country. But the following guidance may upgrade the reasoning and decision making in clinical practice.

- a. Guidance is required for management of Anti HBc positive person.

**Table-I**

*HBV serological test, interpretation and vaccination<sup>34</sup>? (REF)*

Test	Result	Interpretation	Vaccination needed
HBsAg	negative	susceptible	Yes
anti-HBc	negative		
anti-HBs	negative		
HBsAg	negative	Immune due to	no
anti-HBc	negative	vaccination	
anti-HBs	positive with $\geq 10$ mIU/mL		
HBsAg	negative	immune due to natural	no
anti-HBc	positive	infection	
anti-HBs	positive		
HBsAg	positive	chronically	no
anti-HBc	positive	infected	
IgM anti-HBc	negative		
anti-HBs	negative		
HBsAg	negative	five	???
anti-HBc	positive	interpretations	
anti-HBs	negative	possible†	

- b. Anti HBc positive indicates HBV infection of a person; it may be ongoing or previous infection or resolved infection.
- c. Anti HBc positive with HBsAg positive indicates ongoing infection.
- d. HBsAg negative and Anti HBc positive indicate previous infection or resolved HBV infection. High degree of suspicion of chronic liver disease, co infection with other viruses (HCV) and immunosuppressive condition necessitates further evaluation.
- e. HBV DNA screening may be required some special populations with Anti HBc positive condition.
- f. Isolated Anti HBc positive chronic hepatitis C patient on DAA should be monitor for ALT. If ALT is raised despite undetectable HCV RNA; HBV DNA is recommended.
- g. Monitor for reactivation by HBsAg and HBV DNA and treat if clinically evident positivity.
- h. Anti viral prophylaxis is recommended over monitoring. Treatment should be continued for 6 months after discontinuation of immunosuppressive therapy
- j. Prophylactic antiviral therapy is recommended for Isolated Anti HBc total positive (HBsAg negative and anti-HBc positive) patients to prevent reactivation of HBV in moderate to high risk group who are on immunosuppressive therapy. Anti viral therapy should be tTAFTDF or entecavir
- k. Screening for HCC should be strengthened in Anti HBc positive patient with cirrhosis or with Anti HBc and HCV co infection.
- l. Anti HBc is not yet recommended as screening test for HBV in Bangladesh for blood transfusion. It may be included for prevention of transmission of HBV with blood transfusion.
- m. Solid organ transplant recipient with anti HBc positive should continue anti-viral prophylaxis according to their immunosuppressive condition.
- n. Anti HBc testing may be proposed in addition to HBsAg before vaccination of HBV. HBsAg negative, Anti HBs negative necessitates HBV vaccination. HBsAg negative, Anti HBc positive

and Anti HBs positive does not require vaccination. But in case of HBsAg negative, Anti HBc positive and Anti HBs negative may not require vaccination.

#### Conclusion:

Anti HBc positivity is very common in Bangladesh. It includes several spectrums of clinical conditions and related with major issues those have clinical significance. Screening for Anti HBc is mandatory for HBV evaluation, organ transplantation and HCV therapy. Anti HBc is found in different phase of HBV infection, acute, chronic, resolved HBV infection, occult HBV infection. High degree of suspicion of HBV infection with ongoing chronic liver disease in absence HBsAg requires further evaluation. HBV DNA testing and anti viral therapy for HBV is necessary during immunosuppressive therapy. Anti HBc screening should be included for blood transfusion and HBV vaccination.

#### Acknowledgements:

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