Editorial

Entity and clinical utility of anti-HBs for prevention, control and management of hepatitis B virus infection

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Introduction

Hepatitis B virus (HBV), a member of the family hepadnaviridae, is non-cytopathic virus. More than 2 billion people-one third of world's population have been infected with HBV at some point in their life. Of those infected with HBV, 350-400 million remain chronically infected, and an estimated 1 million die of HBV-related liver diseases annually.

Important insights about epidemiology, virology, immunology, and pathogenesis of HBV have been documented during the last 4 decades. Prophylactic vaccines against the HBV have been developed in 1980s. In 1992, the World Health Organization (WHO) recommended that childhood hepatitis B vaccination be included in immunization program of all countries. Preventive vaccine using hepatitis B surface antigen (HBsAg) alone or combined with other antigens allow for the generation of neutralizing antibodies, antibody to HBsAg (anti-HBs), which effectively prevent HBV infection in immunocompetent HBV uninfected individuals. Thus, presence of anti-HBs in the sera is regarded as a marker of protection from HBV infection.

However, recent developments about molecular characteristics of the HBV infection and immune responses against various HBV-related antigens indicate that the protective role of anti-HBs and their clinical implications should be re-assessed. Also, anti-HBs related information should be transmitted to various authorities related to prevention, control and management of HBV infection-such; general physicians, hepatologists, gastroenterologists, oncologists, rheumatologists, pathologists, public health personnel, and policy makers. In addition, some comprehensive information about anti-HBs should be transmitted to general population, especially those of developing countries of Asia and Africa.

Conventional Wisdom about HBsAg and Anti-HBs

HBsAg is regarded as the gold standard of HBV infection in most developing countries. HBsAg is checked to assess if one is infected with the HBV or not. HBV DNA is not checked in most developing countries. The protective role of anti-HBs against HBV is well-documented. Different people related with health care deliver system such as physicians, academicians and public heath personnel agree about this. Also, protective roles of anti-HBs against the HBV have been accepted by specialists, including hepatologists and gastroenterologists in most developing countries. Thus, if some one expresses anti-HBs in the sera, blood from this person is used for transfusion. Also, anti-HBs bearing subjects are regarded as free from HBV infection and HBV DNA is not checked in these subjects prior to use of immune suppressive drugs or cytotoxic drugs.

In this context, the real clinical and immunological implications of anti-HBs should be properly evaluated. Studies have shown that anti-HBs-positive persons may harbor HBV and transfusion of their blood may induce HBV infection. Also, anti-HBs expressing subjects may be suffering from chronic liver diseases. In addition, treatment with different drugs may allow increased HBV replication in anti-HBs expressing subjects. As there are different faces of anti-HBs, a comprehensive discussion will be made about clinical implications of anti-HBs in different subjects.

Many Faces of Anti-HBs

Anti-HBs in Normal Individuals due to Vaccination with Hepatitis B (HB) Vaccines

This is the most common method of induction of anti-HBs in normal subjects. Usually, detectable levels of anti-

HBs can be found in about 90%-95% normal individuals (without previous HBV infection) due to vaccination with HB vaccines. The titers of anti-HBs may exhibit fluctuations in these subjects. Also, anti-HBs may become undetectable along with time. However, a booster injection with HB vaccine would soon restore serum anti-HBs levels in these subjects. In addition, HBsAg-specific cellular immune responses may have protective role against the HBV in normal HB vaccine immunized subjects, even if the levels of anti-HBs are decreased with time.

Anti-HBs in HBV-Infected Patients without Subjective Symptoms of Hepatitis

Anti-HBs may be developed spontaneously in the sera of some HBV-infected subjects. These subjects usually develop no symptoms of acute hepatitis or jaundice. HBV infection is detected in these subjects incidentally when that is checked for reasons other than liver diseases or during periodic health check up. This may be especially dominant in some endemic areas of HBV infection, such as Bangladesh. Thus, some anti-HBs expressing subjects may have infected with the HBV and possibly harboring HBV in the liver or other organs.

Anti-HBs in Patients with Resolved Acute Hepatitis B

One of the characteristic features of resolved acute hepatitis B is development of anti-HBs in the sera after one episode of acute hepatitis. These patients are infected with HBV, express HBsAg and develop symptoms of acute hepatitis including jaundice. In course of time, they become negative for HBsAg. Subsequently, anti-HBs are developed in their sera. Anti-HBs may persist in these patients for life or the titers of anti-HBs may wane along with time. However, many of these patients also harbor low levels of HBV DNA in the liver or other organs.

Anti-HBs in Patients with Chronic Hepatitis B

Anti-HBs can also be detected in patients with CHB, but, this is not a normal phenomenon. In addition, anti-HBs may not be detected in these patients by conventional estimation procedures. These patients express HBV DNA, HBsAg and anti-HBs.

Anti-HBs in the Sera and their Clinical Implications

Thus, anti-HBs may be found in normal individuals due to immunization with HB vaccine, or anti-HBs may be detected in some persons as a result of HBV infection. The clinical significance of anti-HBs in HB vaccinated individuals and in HBV-infected subjects is not same. Understandings of different cellular and molecular events that lead to development of anti-HBs in different subjects are extremely important to develop insights about control and management of HBV. Assessment of HBV DNA in the sera usually provides more insight about clinical implications of anti-HBs. However, estimation of HBV DNA is costly and may be done only in highly specialized laboratory of Bangladesh. This is more relevant in developing countries that have few laboratories capable of assessment of HBV DNA. In addition, HBV DNA may be localized mainly in the liver of these patients, and HBV DNA may not be found in the sera. Thus, estimation of HBV DNA in the sera may not be practical and purposeful in many circumstances.

Antibody to Hepatitis B Core Antigen (anti-HBc) and their Clinical Implications

As a practical approach, anti-HBc may be evaluated in the sera of different subjects before blood donation or treatment with immunosuppressive drugs. Estimation of anti-HBc is significantly cheaper than that of assessment of HBV DNA. HB vaccinated individuals do not express anti-HBc, but express anti-HBs. On the other hand, patients expressing anti-HBs and anti-HBs have been infected with the HBV, sometime in their life.

Clinical Implications of Anti-HBs without or with Anti-HBc

1. If anti-HBs are detected in a normal individual during routine health check, it is important to determine whether he was vaccinated previously with HB vaccine or not. If one's provides a history of HB vaccination and express anti-HBs, further investigation is not routinely recommended. However, the patient may be infected with the HBV before or after HB vaccination. If possible, anti-HBc should be monitored in these cases also.

2. Patients those are expressing both anti-HBs and anti-HBc have been infected with the HBV at some point of their life. The patient may provide a history suggestive of HBV infection or the infection may have passed unnoticed. Usually, further investigations are not accomplished in these patients. However, the attending physician should have a clear picture about the subjects. These subjects should be properly investigated in circumstances described below:

A. If the individual is a blood donor, then he should be advised not to donate blood any more. This is especially relevant in developing countries of Asia and Africa. HBsAg is usually estimated before blood donation in these countries. However, the sensitivity and specificity of estimation of HBsAg is not satisfactory. There is no nucleic acid testing of donor's blood in most of these countries. Thus, blood of these persons may induce HBV infection to the recipients. Patients harboring both anti-HBs and anti-HBc may contain HBV DNA in their blood and transfusion of their blood can cause HBV infection in recipients.

B. If the patient expressing anti-HBs and anti-HBc are going to have immune suppressive drug for treatment of other diseases, there may be serious consequences if these patients are not properly evaluated about the HBV. These patients harbor either small amounts of replicating HBV DNA or non replicating forms of cccDNA in the liver. Thus, they may be HBV DNA negative in the sera. But, HBV DNA would be detected in the liver. Administration of immunosuppressive drug may cause of flare of HBV replication that may cause severe or fulminant hepatitis in these patients. If they need immunosuppressive drugs, preparation should be taken to suppress increased HBV replication by antiviral drugs. The patients should be regularly followed up for flare up of HBV DNA. Other measures may be needed to tackle these patients.

Practical Management of Anti-HBs Expressing Subjects

1. There is a need to take a detailed history of these subjects. If the subject provides a history of HB vaccination, he should be explained that although anti-HBs are a marker of protection against HBV infection, he should be cautious during blood donation and use of different drugs. The patient should disclose about his anti-HBs status during visit to another physician.

2. The subject may be checked for anti-HBc, and if possible for HBV DNA, to develop insights about his HBV status. This should not be a routine testing, but, may be done after careful judgments by the physicians.

3. If one is anti-HBs positive without any history of HB vaccination, it is to be assessed if the patient is a candidate of resolved acute hepatitis B or a chronic HBV carrier. This can be judged by estimating anti-HBc and HBV DNA. Also, parameters of liver function test should be evaluated in these subjects. On this basis of these data, further investigations including liver biopsy, may be needed in these subjects.

4. If the patient is a subject of acute resolved hepatitis B or chronic HBV carriers, he should be explained that he or she have been harboring HBV either in silent form or in mild or moderately active form. The patients should be provided due advice and management by the attending physicians. The patients should also be advised to describe his HBV status when visiting to another physician due to other pathological conditions.

Concluding Remarks

Anti-HBs represent the protective antibody against HBV. Presence of anti-HBs in the sera implies that the subjects are not prone to be infected by HBV. However, it is also be remembered that anti-HBs expressing subjects are not completely protected from HBV infection. This script has been compiled because anti-HBs have been described as definitive protective marker of HBV infection in medical curriculum of most countries. Unfortunately, the clinical implications of anti-HBs have not been updated to undergraduate medical students, general physicians, and specialists of different fields in developing countries. Indeed, this information is constantly updated in developed and advanced countries. The purpose of this communication is not to make a panic by down regulating the protective role of anti-HBs in the context of HBV infection. This article is to provide new and updated information to physicians of developing countries about significance of anti-HBs. In addition to hepatologists, the clinical implications of anti-HBs should be updated by specialists of other branches of medicine, such as rheumatologists, oncologists, and hematologists. These physicians may use immunosuppressive drugs for treating various pathological conditions. About 8-10 million of Bangladeshi's are chronically infected with the HBV. Accordingly, any therapeutic maneuvers that alter the kinetics of HBV including anti-HBs deserve constant visiting and revisiting. Also, lack of attention regarding limitations of HBsAg and anti-HBs may be related with occurrence of new cases of acute HBV infection at Bangladesh.

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