Management of Occult HBV Infection

Seyed Moayed Alavian
Professor of Gastroenterology and Hepatology
Editor in-chief of Hepatitis Monthly
E mail: editor@hepatmon.com

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Introduction

Introduction

- The presence of a**nti-HBc** is now recognized not only as a valuable marker of prior exposure to HBV, but also as a **sentinel marker for OBI**.
- Nevertheless, *over 20%* of individuals with OBI are **negative for all HBV infection serum markers**, while either antibody titres become undetectable over time, or seroconversion may never occur.
- Therefore, the **HBV-DNA** may become the single marker of HBV infection and it can be detected at low levels (**<200 IU/mL**).

Zobeiri M. Occult hepatitis B: clinical viewpoint and management. Hepat Res Treat. 2013
Vitale F, et al. Can the serological status of anti-HBc alone be considered a sentinel marker for detection of occult HBV infection? J Med Virol. 2008

Geographical variations

- The finding of HBV DNA in samples from HBsAg-seronegative patients showed remarkable geographical variations , previous studies in high prevalence areas found that up to **30%** of Chinese patients and **50%** of Japanese patients with serological markers of past HBV infection had detectable HBV DNA.

Alavian SM, Nematizadeh F. Occult HBV infection in patients with serological markers of past HBV infection. Am J Gastroenterol. 2003

Clinical Setting

OBI may have an impact in different clinical settings

- Exposure to OBI may lead to HBV infection through the following routes: **blood transfusions**, **hemodialysis** and **organ transplantation**, causing classical forms of hepatitis B in the newly infected individual.
- OBI increases the risk of liver fibrosis progression and the development of hepatocellular carcinoma (HCC).
- Conditions resulting in immune deficiency, such as chemotherapy or HIV infection, increase the risk of viral reactivation in OBI, leading to more severe HBV cases, and increasing the mortality rate up to 20%.

Lledo JL, et al. Management of occult hepatitis B virus infection: an update for the clinician. World J Gastroenterol. 2011

Scenarios in which occult hepatitis B virus infection is of clinical importance

- After acute hepatitis B
- Blood donation
- Organ transplantation
- Immunosuppression
- Cryptogenic chronic liver disease
- Hepatocellular carcinoma development

Lledo JL, et al. Management of occult hepatitis B virus infection: an update for the clinician. World J Gastroenterol. 2011

OBI after Acute Hepatitis

- Patients who have recovered from acute hepatitis B might carry HBV genomes even after the seroconversion to anti-HBs for several years without showing any clinical or biochemical evidence of liver disease.
- In conditions of immunocompetence, OBI is innocuous in itself, but when other relevant causes of liver disease are present, mild liver damage produced by the occult virus might contribute to making the course of the liver disease worse.
- The replication of HBV may persist in some organs, most likely in the liver or peripheral blood cells, for a long period after recovery from acute hepatitis B, and the data indicate the possible transmission of HBV from organ transplantation donors who exhibit serological markers of past infection only.

Yotsuyanagi H, et al. Persistent viremia after recovery from self-limited acute hepatitis B. Hepatology. 1998
Raimondo G, et al. What is the clinical impact of occult hepatitis B virus infection? Lancet. 2005

Occult hepatitis B virus infection: implications in transfusion

- Donations negative for HBsAg, but positive for HBV DNA, with or without the presence of HBV antibodies, correspond to 'occult' HBV infection (OBI).
- The frequency of OBI depends on the relative sensitivity of both HBsAg and HBV DNA assays. It also depends on the prevalence of HBV infection in the population.

Allain JP. Occult hepatitis B virus infection: implications in transfusion. Vox Sang. 2004

Occult hepatitis B virus infection: implications in transfusion

- The critical question is whether or not OBI is infectious by transfusion. All forms have been shown to be infectious in immunocompromised individuals, such as organ- or bone marrow-transplant recipients. In immunocompetent recipients, there is no evidence that anti-HBc-containing components (even at low titre) are infectious.

Allain JP. Occult hepatitis B virus infection: implications in transfusion. Vox Sang. 2004

OBI AND Blood Donations

- HBsAg-negative blood donations that contain HBV DNA are considered infectious and might transmit HBV that usually induces typical type B hepatitis in recipients.
- Nowadays, OBI is the major cause of post-transfusion hepatitis B in western countries.
- In immunocompetent humans who have developed anti-HBc and anti-HBs following acute hepatitis B, no transmission of HBV has ever been demonstrated in blood donations.
    - **The risk of transmission is high with blood that lacks anti-HBs**
- **The caution is recommended when immunodeficient patients receive anti-HBc-positive, anti-HBs-positive donations**

Hollinger FB. Hepatitis B virus infection and transfusion medicine: science and the occult. Transfusion. 2008

OBI AND Blood Donations

- There are several possible explanations as to why **not all recipients** of HBV-DNA-positive, HBsAg-negative blood develop hepatitis:
- Vaccination or prior disease in recipients can induce immunity to HBV
- Concurrent infusion of anti-HBs in another blood component
- Presence of immune complexes
- Inocula below the minimum infectious dose of HBV
- Presence of defective or replication- incompetent virions
- Viral interference from another pathogen

Candotti D, et al. Transfusion-transmitted hepatitis B virus infection. Journal of hepatology. 2009

OBI AND Blood Donations

- **NAT** detects potentially infectious blood units before donation and consequently **reduces the risk** of transmitting HBV through blood transfusion.
- In **HBV-endemic regions** of the world, where a universal hepatitis B vaccination program is not available, NAT has higher potential benefit for reducing this risk. However, in **low-prevalence countries**, the availability of highly sensitive and specific HBsAg and anti-HBc assays limits the benefit of NAT.

Hollinger FB. Hepatitis B virus infection and transfusion medicine: science and the occult. Transfusion. 2008

OBI and Organ Transplantation

- Grafts from donors who are **HBsAg-negative and anti-HBc-positive** might transmit HBV to recipients after organ transplantation; particularly in the case of **orthotopic liver transplantation** (OLT), and especially if the recipient is negative for all HBV serum markers, because of the presence of viral strains in the hepatocytes, which can be reactivated during immunosuppression.

Dickson RC, et al. Transmission of hepatitis B by transplantation of livers from donors positive for antibody to hepatitis B core antigen. The National Institute of Diabetes and Digestive and Kidney Diseases Liver Transplantation Database. Gastroenterology. 1997

OBI and Organ Transplantation

- Reactivation of OBI is possible in liver transplant recipients with a serological profile of past exposure to hepatitis B (anti-HBc positive), as a consequence of immunosuppression after transplantation.

- Prophylaxis with antiviral agents prevents reactivation of OBI in most of these cases, it is not known if prior hepatitis B immunization with an optimal anti-HBs response can modulate or abort the infection.

Samuel D, et al. Report of the monothematic EASL conference on liver transplantation for viral hepatitis. J hepatol. 2006

OBI and Organ Transplantation

- The risk of occult HBV transmission is very low after kidney, heart or bone marrow transplantation.

De Feo TM, et al. Risk of transmission of hepatitis B virus from anti-HBC positive cadaveric organ donors: a collaborative study. Transplant Proc. 2005

OBI and Organ Transplantation

- Hepatitis B infection usually has a **benign course** and is often **less severe** following solid organ transplantation obtained from anti-HBc positive donors when compared to hepatitis B that develops as a result of recurrent disease.

Douglas DD, et al.The clinical course of transplantation-associated de novo hepatitis B infection in the liver transplant recipient. Liver Transpl Surg. 1997

Reactivation OF OBI

The risk of HBV reactivation is well documented in **HBsAg-positive** patients who receive **chemotherapy** and/or with **hemato-oncologic diseases**, and there is consensus that these patients require prophylaxis with an antiviral agent.

The risk of HBV reactivation in **OBI is less defined** . The state of strong suppression of viral replication and gene expression activity by the host immune system in OBI patients might be discontinued, which leads to the development of a classical hepatitis B that often has a **severe clinical course**

This situation has been observed in several conditions including **HIV** infection, **hematological malignancies**, patients undergoing **chemotherapy**, **transplantation** (bone marrow, or liver, and treatment with potent **immunosuppressive drugs** like rituximab (anti-CD20), alemtuzumab (anti-CD52) or infliximab (anti-tumor necrosis factor).

Lledo JL, et al. Management of occult hepatitis B virus infection: an update for the clinician. World J Gastroenterol. 2011

Reactivation OF OBI

All patients who receive chemotherapy and immunotherapy should be tested for HBV serology and/or viremia before starting therapy, especially if they are positive for HBc Ab, and monitored for several months after stopping treatment.

- ✓ Early identification of virological reactivation is essential to start antiviral therapy and prevent the occurrence of hepatitis B, which can be very dangerous in these patients

Patients who are HBV-DNA-negative and anti-HBc-positive should:

- ✓ Monitor at 4-wk intervals with HBV-DNA NAT (low limit of detection < 10 IU/mL) and begin antiviral therapy when the result is > 30 IU/mL
- ✓ Monitor at 4-wk intervals with a highly sensitive HBsAg assay (low limit of detection < 0.1 ng/mL) and begin antiviral therapy when the test becomes positive.

•For those with OBI, especially in the absence of anti-HBs, a prudent therapeutic approach is to initiate HBV antiviral therapy (lamivudine, or tenofovir) prior to chemotherapy.

Lledo JL, et al. Management of occult hepatitis B virus infection: an update for the clinician. World J Gastroenterol. 2011

Reactivation in Occult HBV Undergoing High-Risk Immunosuppressive Therapy-role of Serum HBcrAg

- One hundred and twenty-four HBsAg-negative, anti-HBc-positive patients (rituximab, N=62; allogeneic hematopoietic stem cell transplantation , N=62) with a median follow-up of 64 weeks (range: 4-104 weeks) were studied. HBV reactivation occurred in 31 patients, with a 2-year cumulative reactivation rate of 40.4%.

- **Serum HBcrAg** positivity is a significant risk factor of HBV reactivation in HBsAg-negative, anti-HBc-positive patients undergoing high-risk immunosuppressive therapy and can potentially have a role in identifying patients who will best benefit from prophylactic nucleoside analogue treatment

Seto WK,, et al. Association of Hepatitis B Core-Related Antigen With Hepatitis B Virus Reactivation in Occult Viral Carriers Undergoing High-Risk Immunosuppressive Therapy. Am J Gastroenterol. 2016.

OBI has been detected in patients with cryptogenic chronic liver disease

•In a study in 65 consecutive paraffin-embedded liver tissues from cases by HBV DNA, we found that the frequency of occult HBV infection in cryptogenic cirrhosis was more than **50% in Iran**.

HBsAg negativity per se is insufficient for exclusion of HBV infection, and screening for occult HBV infection by HBV-DNA assay is necessary before diagnosis of cryptogenic cirrhosis.

Close monitoring of serum HBV-DNA levels and liver-enzyme levels could be useful in the management of patients with OBI and cryptogenic liver disease in two respects:

(1) To predict the risk of cirrhosis or HCC

(2) To decide on the possibility of antiviral treatment to prevent HBV reactivation or transmission in the case of transplantation.

Honarkar Z, **Alavian SM,** Samiee S, Saeedfar K, Baladast M, Ehsani MJ, et al. Occult Hepatitis B as a cause of cryptogenic cirrhosis. Hepat Mon. 2004;

Chemin I, et al. Close monitoring of serum HBV DNA levels and liver enzymes levels is most useful in the management of patients with occult HBV infection. Journal of hepatology. 2009

OBI and HCC Development

- OBI is a potential risk factor for HCC development. OBI seems to maintain HBV oncogenic mechanisms such as the capacity to be integrated in the host genome, and production of transforming proteins. This pro-oncogenic role is not only the consequence of the integration of viral DNA into the host genome.

It is recommended for testing all HBsAg-negative patients with HCC for OBI.

Zobeiri M. Occult hepatitis B: clinical viewpoint and management. Hepat Res Treat. 2013

Occult Hepatitis B Infection in Chronic Hemodialysis Patients: Current Concepts and Strategy.

- A variation in the prevalence of OHB in hemodialysis patients in different parts in the wrold has reported as; North American population: 3.7%
- 4.9% in India, In Italy, the prevalence ranged from 0% in a large cohort of 213 dialysis patients to 26.6% in another cohort while in Turkey prevalence rates of 2.7% and 12.4% have been recorded.
- Limited information on the clinical impact and therapeutic management of OHB in chronic hemodialysis patients.

Hollinger FB, Habibollahi P, Daneshmand A, **Alavian SM**. Occult Hepatitis B Infection in Chronic Hemodialysis Patients: Current Concepts and Strategy. Hepat Mon. 2010

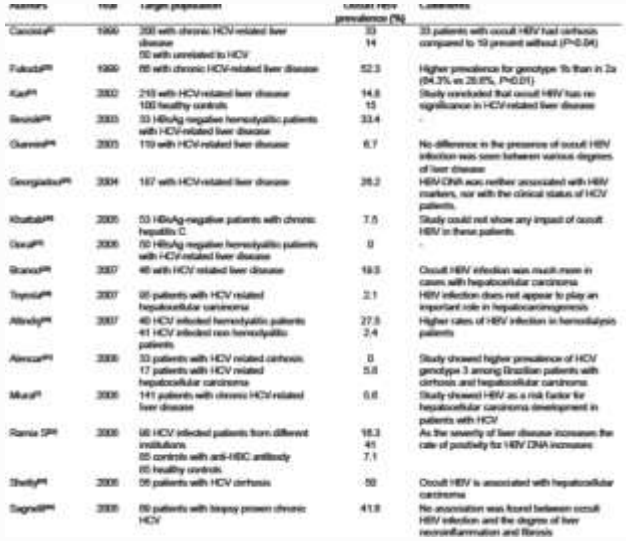
Occult hepatitis B virus infection: clinical implications in tuberculosis treatment

- A high OBI prevalence among TB patients suggests screening for HBV-DNA.
- OBI as an important drug-induced liver injury (DILI) predictor(HR 2.98, 95% CI 1.30-6.86) , requiring routine HBV-DNA testing during TB treatment, especially in TB/HIV/OBI co-infected
- Therefore, HBV-DNA testing should be considered routinely in monitoring drug-induced liver injury , and also in other clinical implications associated with OBI, reduce morbidity and mortality.

- Trigo C, et al. Occult hepatitis B virus infection: clinical implications in tuberculosis treatment. J Viral Hepat. 2016.

Occult HBV Infection and its Possible Impact on Chronic HCV Infection

- Occult HBV infection has been reported in different populations, especially among patients with **HCV** related liver disease.
- There is a possible correlation of occult HBV with **lower response to anti-viral treatment**, **higher grades of liver histological changes**, and also developing **hepatocellular carcinoma**.
- In Our experience in Iran in chronic hepatitis C patients studied, HBVDNA was detectable by PCR in **19%**.



Habibollahi P, Safari S, Daryani NE, **Alavian SM.** Occult hepatitis B infection and its possible impact on chronic hepatitis C virus infection. Saudi JGastroenterol. 2009

Aghazadeh R, Honarkar Z, **Alavian SM**, et al. Occult HBV Infection among Chronic Hepatitis C patients. Shiraz E-Med J. 2006

Conclusion

We, gastroenterologists, infectious disease specialists, need to more clinical data from different groups for OBI and impact of it on outcomes, We need a collaboration with virologists and immunologists and Basic science departments