

# DIAGNOSIS AND MANAGEMENT OF OCCULT HEPATITIS B VIRUS INFECTION: A SHORT REVIEW

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## ABSTRACT

Occult hepatitis B virus infection (OBI) is a challenging clinical entity. It is defined as the presence of viral DNA in the liver or serum of subjects who test negative for the hepatitis B surface antigen. Molecular evidence of OBI consists of covalently closed circular DNA persisting in the nuclei of hepatocytes after infection. Immunocompetent individuals have a lower risk of complications than immunosuppressed subjects. However, under certain scenarios, OBI acquires clinical manifestations that include transmission of the infection via blood or organ transplantation, chronic liver disease progression, hepatocellular carcinoma, and virus reactivation when a state of immunosuppression develops. This review updates the clinical aspects of the diagnosis and management of OBI.

Keywords: Occult hepatitis B virus infection, diagnosis, management.

## INTRODUCTION

Hepatitis B virus (HBV) infection is a global health problem. Estimates indicate that around a third of the world's population have past or present HBV infection with 350 million persons chronically infected.<sup>1</sup> The clinical spectrum of chronic HBV infection ranges from a healthy carrier state to more advanced liver disease (LD), such as cirrhosis or hepatocellular carcinoma (HCC).<sup>1,2</sup> HBV infection is effectively the leading cause of cirrhosis and HCC worldwide.<sup>2</sup> During the natural course of HBV infection, constant interaction between host factors (immune system) and the virus serves to explain the different stages of HBV infection: immune tolerance, immune clearance, inactive carrier state, reactivation stage, and hepatitis B surface antigen (HBsAg)-negative (occult) stage. These stages are not necessarily unidirectional, sequential, and stable, and any changes in the immune system and/or HBV can modify the state of infection.<sup>1-3</sup> The stages leading to occult HBV infection (OBI) have been widely addressed. This review focuses on the occult stage of HBV infection and discusses present knowledge of its definition, diagnosis, clinical scenarios, and management.

## DEFINITION

OBI is defined as the presence of the HBV genome in the liver tissue of patients, with detectable or undetectable serum HBV DNA, who test negative for HBsAg.<sup>4</sup> The molecular rationale for OBI is the conversion of HBV DNA to covalently closed circular DNA (cccDNA). After binding to different proteins, cccDNA becomes a stable and durable mini-chromosome that persists indefinitely within hepatocyte nuclei.<sup>5</sup>

Two different serological patterns of OBI have been defined according to detected serum markers of HBV.<sup>4</sup> This includes seropositive OBI, which represents 80% of cases. This term is used to describe OBI patients who test positive for the anti-hepatitis B core antibody (anti-HBc) and/or for the anti-hepatitis B surface antibody (anti-HBs), yet lack detectable HBsAg in serum. This situation may arise when acute hepatitis B resolves after months of HBsAg carriage, or when, after years of chronic HBsAg positive infection, the patient tests negative for the antigen. Along with seronegative OBI, which represents 20% of cases. These patients test negative for both antibodies (anti-HBc and anti-

HBs) and usually only very low levels of HBV DNA are detected. This serological pattern may reflect the time between infection and the detection of antibodies known as the 'window period' (pre-seroconversion), or clearance of hepatitis B antibodies. This seronegative OBI pattern should always be considered, since any person lacking serum HBV antigens or antibodies could be a seronegative OBI patient.

## PREVALENCE

The prevalence of OBI is difficult to assess and varies according to factors such as: endemic disease level, sub-population examined, the methods used to assess OBI, or tissue tested (liver versus serum).<sup>6</sup> In the following sections, we describe reported OBI prevalence for the different populations examined to date.

The transmission route for HBV and hepatitis C virus (HCV) is similar in that a high prevalence of OBI may be expected in HCV patients. Effectively, HCV patients show the highest reported prevalence of OBI. In one study, it was detected that 33% of HCV patients had OBI compared to 14% of controls.<sup>7</sup> However, the impact of OBI in patients with HCV remains unclear. It has so far been established that OBI worsens the clinical course of HCV infection, as more inflammatory activity, more fibrosis, and an increased rate of cirrhosis and HCC have been observed in HCV patients with OBI.<sup>8,9</sup>

Risk factors for a haemodialysis patient to develop OBI include an increased number of blood transfusions, frequent invasive procedures, and immunosuppression. Several studies have shown that 0-36% of patients on haemodialysis, and nearly 10% of patients on continuous ambulatory peritoneal dialysis, suffer from OBI.<sup>6,10</sup> Reported OBI prevalence in HIV patients have been 0-89%.<sup>11</sup> This wide range reflects difficulties in assessing OBI. The pathological explanation could be cellular immune deficiency (decreased CD4).<sup>11</sup> There is little evidence linking LD of unknown origin to OBI. However, some authors report that 19-31% of patients with cryptogenic LD present with OBI.<sup>12,13</sup> OBI prevalence in blood donors varies among the United States, Europe, and Asia. In Europe, despite improvements in screening for blood donation, HBV DNA is detected in 0-1.6% of cases.<sup>6</sup> Thus, HBV remains the most frequent transfusion-transmitted viral infection.

Few studies have examined this issue in the general population. In one study, OBI was detected in 18% of subjects with serological evidence of previous HBV infection and in 8% of HBV seronegative individuals.<sup>13</sup> Other authors have reported similar prevalence. Despite a lack of data, we would expect high variation among different populations.

## DIAGNOSIS

OBI is diagnosed when HBV DNA is detected in the liver or in blood samples of patients who test HBsAg negative.<sup>2,4</sup> Although the gold standard is liver tissue testing, this is not usually feasible; most often the diagnosis of OBI is based on the results of a blood test.<sup>14</sup> However, there is frequent discrepancy between the detection of HBV DNA in the liver or blood. Usually, when a blood sample tests positive for HBV DNA, a liver sample will also return a positive result, but the reverse is not always true. Thus, HBV DNA may be detected in the liver, but not necessarily in blood. Of course, since HBV DNA occurs inside the nuclei of hepatocytes, if a liver sample is negative for HBV DNA, a blood sample will also be negative.<sup>14</sup>

It is important to define the optimal methodology to quantify HBsAg and HBV DNA.<sup>14-16</sup> Most HBsAg commercial assays are able to detect all genotypes and subtypes of the wild-type virus, but some may miss mutations in the S region. Hepatologists should bear this in mind, because some patients might be diagnosed with OBI, when they only have an undetectable mutation in their HBsAg (false OBI).<sup>16</sup> To detect HBV DNA, it is very important to use a highly sensitive and specific assay because OBI is usually associated with low levels of HBV DNA. An international consensus<sup>3</sup> introduced a cut-off value for serum HBV DNA (<200 IU/ml). This means that cases of individuals whose HBV DNA levels are similar to those with evident overt HBV infection are generally due to infection with HBV-escape mutants and should be labelled as 'false OBI'.<sup>2</sup> It is recommended that the assay has a detection limit of <10 copies/ml. With current technologies (nested-polymerase chain reaction (PCR), real time-PCR, and transcription based mediated amplification), it is possible to reduce the lower detection limit to >5 copies/ml, which clearly improves sensitivity.<sup>15,16</sup>

The use of anti-HBc antibody for OBI diagnosis has been addressed in some studies. This is the first antibody to appear. It is considered a sign of active or past infection depending on the other HBV

serum markers. It can be found in almost every patient with a previous contact with HBV, even in HBV carriers without other responses.<sup>17</sup> Despite not being an ideal marker, the risk of occult hepatitis associated with anti-HBc seropositivity has been demonstrated extensively, and the presence of anti-HBc antibodies can be considered a sentinel marker of occult HBV infection.<sup>18</sup> In fact, it has been recommended by a panel of experts as a surrogate marker to identify potential seropositive OBI patients when sensitive HBV DNA tests are not available.<sup>4</sup> Hepatologists should nonetheless be aware that the absence of this antibody (anti-HBc) does not rule out OBI (seronegative-OBI).

## MANAGEMENT

The clinical significance of OBI has not been fully established. However, OBI should be carefully assessed in certain clinical scenarios: HBV infection transmission (via blood transfusion or solid organ transplantation), LD progression, HCC onset, and HBV reactivation (Figure 1).

### Risk of Transmission

Blood transfusion. The introduction of sensitive assays has meant that HBV transmission through blood transfusion is a rare event. However, some subjects who screen negative for HBV in the

usual serum marker test, could be at risk for HBV transmission. These are: a) seronegative OBI patients (who test negative for all antigens and antibodies, yet have DNA detectable in blood), and b) patients infected with an S-escape mutant virus that is able to actively replicate but whose mutant HBsAg is not detected by routinely available diagnostic assays. This is the most frequent situation leading to cases of hepatitis B related to blood transfusion.<sup>19</sup>

Today, OBI is the main cause of post-transfusion hepatitis B. Hence the risk of transmission is probably greater than for HCV or HIV. However, not all patients transfused with blood containing HBV DNA will suffer from hepatitis B, due to previous vaccination of the recipient, immune complexes, presence of defective virions, transient periods of viraemia in OBI patients, etc. Recipients with anti-HBs antibodies make the possibility of transmission insignificant, although the cut-off level of these antibodies is still a matter of debate.<sup>20</sup>

Some studies have shown that the frequency of serum HBV DNA positivity in HBsAg negative donors is related to HVB prevalence, which differs between countries and clearly affects serum markers for screening.<sup>20</sup> The management of these patients and ways to screen samples differ between world regions, and the type of suspect patient.

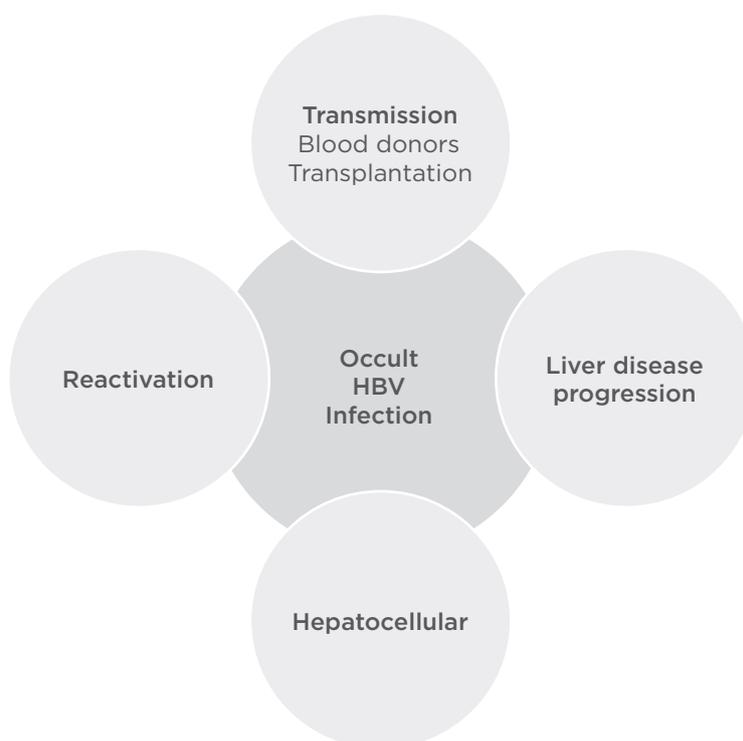


Figure 1: Current clinical scenarios related to occult hepatitis B virus (HBV) infection.

The use of anti-HBs antibodies in HBsAg assays is strongly recommended to detect false OBI patients. In cases of pre-seroconversion period donation (HBsAg and anti-HBc negative), only HBV DNA detection serves to diagnose OBI. In regions where the prevalence of HBV is high (usually coincidental with low-level vaccination areas), OBI may be detected using nucleic acid amplification techniques. In countries with a low prevalence of HBV, screening based on sensitive HbsAg and anti-HBc assays appears to be sufficient.<sup>4,19,20</sup>

**Organ transplantation.** As a consequence of virus reactivation during immunosuppression, grafts from HBsAg negative and anti-HBc positive donors can transmit HBV to recipients.<sup>21,22</sup> This risk is particularly high in liver transplantation compared to kidney, heart, or bone marrow transplantation, and is also greater in recipients testing negative for all serum HBV markers. It is uncertain how many HBV infections following transplant are really *de novo* or transmitted from seronegative OBI donors.<sup>21,23</sup>

The management of these patients is not clearly established. What has been determined is that immunisation prior to transplant creates an anti-HBs antibody response that can modulate or abort infection. Moreover, prophylaxis in HBsAg-negative transplanted patients receiving livers from anti-HBc-positive donors prevents the efficient reactivation of OBI.<sup>24</sup> Immunoglobulin alone or in combination with lamivudine has been used for many years, although lamivudine monotherapy may be similarly efficient yet more cost-effective.<sup>25,26</sup> More recent evidence suggests that the new nucleotide analogs (tenofovir and entecavir) can also be used to prevent the reactivation of HBV.<sup>27</sup> Despite these advances, prophylaxis cannot always prevent HBV infection or reactivation, and there is much debate over whether OBI can impact the long-term outcome of orthotopic liver transplantation (OLT).<sup>22,28</sup> A possible role of OBI has been proposed in progression of post-OLT LD to cirrhosis in patients with HCV infection.<sup>24</sup>

### Risk of Disease Progression

**Chronic LD progression.** OBI per se is thought to be inoffensive in immune-competent individuals, but if other causes of LD co-exist, then minimal lesions produced by OBI infection might negatively influence the outcome of the disease.<sup>8,9</sup>

OBI is observed in patients with cryptogenic chronic LD, suggesting its possible aetiologic

role.<sup>12,13</sup> HBV genomes may persist over time in the liver of subjects who have recovered from self-limited acute hepatitis.<sup>29,30</sup> It has been reported that these OBI patients show normal liver enzyme activity, but their biopsies show a mild necroinflammation that may persist for years and possibly lead to liver fibrosis and the development of cryptogenic cirrhosis.<sup>6</sup> In effect, the results of a recent meta-analysis suggest that OBI is linked to disease progression in HCV cirrhotic patients, enhanced inflammatory activity, augmented fibrosis and cirrhosis, higher anti-HCV antibodies titres, a reduced sustained virological response, and an increased risk of HCC. In addition, more LD-related deaths observed in HCV patients with OBI than those without OBI.<sup>8,9,31,32</sup> However, these findings have been disputed by other authors. Thus, current available data do not support a conclusive role of OBI in LD progression or even related it to a worse outcome in patients with HCV.<sup>6</sup> Well-designed large prospective studies with homogeneous cohorts and uniform selection criteria are needed to determine the true impacts of OBI in HCV patients.

**HCC.** HBV is an oncogenic virus clearly related to HCC development. Both epidemiological and molecular studies have identified correlation between OBI and HCC. The hypothesis is that when the virus persists as OBI, both direct and indirect HBV oncogenic mechanisms are maintained. HBV acts directly via the integration of viral DNA into the host genome, and indirectly through persistent necroinflammation produced by viral replication with effects on the progression of other LDs as previously detailed.<sup>32,33</sup> In a recent meta-analysis, OBI emerged as an important risk factor for HCC development regardless of HCV.<sup>33</sup> OBI could explain HCC in patients with no known LD. However, more work is needed to elucidate the relationship between OBI and HCC development. In the meantime, there is insufficient evidence to justify testing for OBI in HBsAg-negative patients with HCC.<sup>32-35</sup>

**HBV reactivation.** Occult HBV does appear to be safe in immune-competent subjects.<sup>32</sup> However, these patients will be at risk when immune-suppressed.<sup>1,36-39</sup> Interest in this particular scenario has been triggered by the expanding use of potent immunological therapies, which can induce fulminant hepatitis with a mortality between 20-80%. According to European Association For The Study Of The Liver (EASL) guidelines, all patients scheduled for chemotherapy and/or immunotherapy must be tested for ALT and

HBV DNA before, during, and some months after treatment.<sup>1</sup>

A risk of virus reactivation is well documented in HBsAg-positive patients undergoing chemotherapy for onco-haematologic disease, or other immunosuppressive drugs.<sup>1,37,38</sup> There is consensus support that these patients require anti-HBV prophylaxis with an antiviral agent to prevent viral reactivation.<sup>1,4</sup> However, although less frequent, virus reactivation can also occur in patients with OBI,<sup>32</sup> which have HBsAg-negative. The reactivation has been linked to haemato-oncological malignancy such as leukaemias, lymphomas, and bone marrow transplantation/haematopoietic stem cell transplantation, with 10-50% of reactivations in anti-HBc-positive patients. Chemotherapy, especially if steroids are added to any other chemotherapy schedule, is also related with a probability of reactivation between 40-75%. Potent immunosuppressive drugs (rituximab, alemtuzumab, or infliximab) are related with a risk of reactivation around 25-50% in anti-HBc positive patients. The risk of reactivation in HIV patients is low and does not, at present, justify prophylaxis.<sup>34,38-41</sup>

In patients with OBI testing DNA-negative and anti-HBc positive, there are insufficient data to support routine prophylaxis, and it is recommended that antiviral therapy be delayed until HBV DNA becomes detectable.<sup>37-41</sup> However, this type of

decision should be based on each individual's serologic pattern and treatment risk (Tables 1 and 2). A prudent approach to managing oncological patients with OBI is to initiate antiviral HBV prophylaxis therapy prior to chemotherapy. Lamivudine, despite its low genetic barrier, remains the first choice for the prophylaxis of OBI reactivation because of its low cost and the low or absent level of HBV viraemia in OBI. Prophylaxis should be continued for at least 6-12 months after stopping immunosuppressive treatment. In cases of longer treatments (over 12 months), higher HBV DNA levels, or advanced LD, entecavir, or tenofovir are the agents of choice.<sup>42</sup> In HBV DNA-negative, anti-HBc-positive oncological patients, surveillance testing for HBV DNA and/or HBsAg every 1/2 months is recommended. An exception to endorsing strict surveillance would be the presence of a high-risk situation, such as rituximab treatment, bone marrow stem cell transplantation, or steroids added to the chemotherapy schedule.<sup>38-41</sup> In these cases, the EASL guidelines suggest starting with anti-HBV drugs (lamivudine for therapy <6-12 months, and tenofovir or entecavir if treatment is anticipated to be longer or baseline HBV DNA is above 2,000 IU/ml).<sup>1</sup> The reason for this prudent approach when managing OBI patients and those testing HBV DNA-negative and anti-HBc positive is that antiviral therapy is usually unsuccessful after ALT becomes elevated.

**Table 1: Risk treatments in reactivation of hepatitis B virus.**

High-risk treatments	Medium-risk treatments
Rituximab	Anti-tumour necrosis factor drugs
Treatment of onco-haematological diseases (Non-Hodgkin's lymphoma, Hodgkin's lymphoma, chronic lymphocytic leukaemia, chronic myeloid leukaemia, acute myeloid leukaemia, acute lymphoblastic leukaemia, multiple myeloma, Waldenstrom macroglobulinaemia, plasmacytoma, aplastic anaemia, myelodysplastic syndrome, bone marrow transplantation, breast cancer, lung cancer, nasopharyngeal cancer.)	Thiopurines
Use of steroids at any dose added to any chemotherapy (Cyclophosphamide, chlorambucil, cisplatin, vincristine, vinblastine, doxorubicin, epirubicin, daunorubicin, bleomycin, mitomycin C, actinomycin D, cytarabine, fluorouracil, gemcitabine, thioguanine, alemtuzumab, folinic acid, colaspase, docetaxel, etoposide, fludarabine, interferon, procarbazine.)	Isolated immunosuppressive drugs (azathioprine, methotrexate)

**Table 2: Management of occult hepatitis B virus infection (OBI) in patients treated with immunosuppression.**

Serum markers	DNA	Diagnosis	Risk Treatment	Recommendation
HbsAg <b>negative</b> Anti-HBc <b>positive</b>	<b>positive</b>	OBI	High or Medium	Prophylaxis*
	<b>negative</b>	Past HBV	High	Prophylaxis*
			Medium	Surveillance <sup>^</sup>

\*Lamivudine 2-3 weeks before initiation of immunosuppressive or chemotherapy treatment, until 6-12 months after stopping treatment. In cases of longer treatment, high viral load or advanced liver disease, tenofovir or entecavir are recommended. <sup>^</sup>Test ALT and HBV DNA every 1-2 months.

HBsAg: hepatitis B surface antigen; anti-HBc: hepatitis B core antibody; HBV: hepatitis B virus; ALT: alanine transaminase.

## SUMMARY

OBI is a new challenge in virology. It is diagnosed when HBV DNA is detected in the liver or serum of patients who are HBsAg negative. Molecular evidence of OBI consists of covalently closed circular DNA persisting in the nuclei of hepatocytes after infection. OBI affects HCV and HIV patients, patients on haemodialysis, transplanted patients, patients with other chronic LDs, and also the general population. Immunocompetent subjects

do not seem to suffer from OBI. However, there are certain scenarios where OBI has to be kept in mind. These include organ transplantation, especially liver transplantation, with the risk of transmission of the infection and virus reactivation during immunosuppression. Moreover, OBI is thought to be related with some cases of HCC and progression of chronic LD. OBI is of relevance when patients are immunosuppressed because reactivation can occur clearly affecting the prognosis.

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