Occult Hepatitis B Infection

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Abstract

Occult hepatitis B virus infection (OBI) is defined as the presence of HBV replicative templates in the liver with/without circulating HBV DNA in patients with undetectable hepatitis B surface antigen (HBsAg). The prevalence of OBI is estimated to be ranging from <1 to 18% in general population. Usually, serum HBV DNA level is low and intermittently detected, which does not induce liver damage. However, there are some potential risk for patients. Firstly, OBI has been reported to be associated with the development HCC in patients with chronic hepatitis C in some studies, but other studies did not find such an association. It is still a debating issue whether OBI may accelerate the disease progression toward cirrhosis and the development of HCC in patients with other chronic liver diseases. Secondly, there is potential risk of HBV transmission through blood transfusion from OBI donors. The risk could be minimized by screening the blood products using nucleic acid testing. Thirdly, HBV reactivation from OBI is being increasingly recognized when patients receive potent immune-suppressive therapies including B-cell depleting agents. Although prophylactic antiviral therapy minimizes the risk of HBV reactivation, the best strategy to prevent HBV reactivation in these situations remains to be defined. More research is needed to develop a useful guideline to optimize clinical management of OBI.

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1 Introduction

Occult HBV infection (OBI) is defined as the presence of HBV replicative templates, covalently closed circular DNA (cccDNA) in the liver, with/without circulating HBV DNA in patients with undetectable hepatitis B surface antigen (HBsAg) (Raimondo et al. 2019). Clearance of HBsAg months after acute HBV infection in adults or decades after being chronic HBsAg carriage is usually regarded as a functional cure of HBV infection (Lok et al. 2017). However, despite HBsAg seroclearance, the stable cccDNA in the long-lived hepatocytes is an obstacle to eliminating HBV infection and may lead to the development of OBI. It implies that HBV infection may last even under efficient host immune control.

In most cases of OBI with limited HBV replication and viral protein expression, HBV DNA is usually less than 200 IU/ml, which is usually intermittently detected in serum (Kazemi-Shirazi et al. 2000; Cacciola et al. 1999; Huang et al. 2012; Spreafico et al. 2015; El Chaar et al. 2010). HBV DNA between 200 and 2000 IU/mL is also evidenced in some OBI patients due to the limitation of detecting mutated HBsAg by some commercially available HBsAg assays (Huang et al. 2012; El Chaar et al. 2010; Hou et al. 1995; Chaudhuri et al. 2004; Mu et al. 2009; Torbenson and Thomas 2002). Antiviral therapy is practically not recommended for OBI patients under current international guidelines as viral load <2000 IU/mL is usually not associated with HBV-related liver necroinflammation (Raimondo et al. 2019).

2 Classifications of OBI Patients

OBI patients can be classified as seropositive and seronegative OBI by serological markers (Raimondo et al. 2019). Seropositive OBI is characterized as anti-hepatitis B core antibody (anti-HBc) positive with the presence or absence of anti-hepatitis B antibody (anti-HBs). Seronegative OBI is featured by double-negativity for anti-HBc and anti-HBs and accounts for 1 to 20% of OBI (Cacciola et al. 1999; Torbenson and Thomas 2002). Although it is possible that either no production or gradually reduction of anti-HBc and anti-HBs causes seronegative OBI, the clinical outcomes of seropositive versus seronegative OBI patients are still under investigation.

It has been reported that the rates of detectable HBV DNA among OBI categories are the highest in OBI with anti-HBc alone, followed by OBI positive for both anti-HBc and anti-HBs and seronegative OBI (Brechot et al. 2001; Pisaturo et al. 2020). However, the positive rate of HBV DNA in seronegative OBI patients might be underestimated because examination of HBV DNA is conducted systemically only in few studies.

3 Diagnosis

HBV DNA and HBsAg are common viral markers for OBI diagnosis. Although detection of HBV DNA in the liver is the gold standard for the diagnosis of OBI, determination of HBV DNA and HBsAg in the circulating compartment is practically applied instead because acquisition and examination of blood sample is easier than the liver biopsy specimens.

Measurement of HBsAg in OBI patients using insensitive HBsAg assays may be falsely negative thus resulting in diagnostic error of OBI in patients with overt HBV infection. Currently, the lower limit of the most commercial HBsAg detection assays is 0.05 IU/ml. It is demonstrated that 1 to 48% of HBsAg-negative samples were positive for HBsAg if determined by using high sensitivity assay, which detects both outer and inner epitopes of HBsAg, with the lower limit of 0.005 IU/ml (Seto et al. 2012; Ozeki et al. 2018; Yang et al. 2016). A recently advanced strategy for improving HBsAg detection is measuring the level of HBsAg releasing from the HBsAg-anti-HBs immune complex as well as the free-form HBsAg and the detection limit is 0.0005 IU/mL (Matsumoto et al. 2017). It is found that some OBI patients carry only HBsAg-anti-HBs immune complex and are at higher risk of HBV reactivation after receiving rituximab-containing chemotherapy by this novel assay (Kusumoto et al. 2020).

Similarly, detection of HBV DNA in OBI patients by insensitive HBV DNA assays may also lead to false negativity and thus underestimation of OBI cases. The lower limit of conventional HBV DNA assays is 10 to 20 IU/ml. Because HBV DNA level is usually low and intermittently detected in OBI, it is suggested that measurements of serum HBV DNA at multiple timepoints are needed to ensure the detection of OBI.

Anti-HBc had been used as a surrogate marker in OBI diagnosis (Raimondo et al. 2019). The presence of anti-HBc indicates the previous infection of HBV, whereas the presence of anti-HBs alone may denote the previous vaccination of HBV. It has been reported HBV reactivation occurs in HBsAg-negative and anti-HBc-positive individuals with undetectable HBV DNA in the blood (Yang et al. 2018; Huang et al. 2013; Seto et al. 2014). However, the presence of anti-HBc does not equal OBI because evidencing viral replication is mandatory for OBI diagnosis. Accordingly, patients with HBsAg-negative and anti-HBc-positive are better characterized as resolved hepatitis B.

In summary, the major limitation to diagnose OBI is the lack of standardized and validated assays. Therefore, data across different studies cannot be properly compared or integrated.

4 Epidemiology of OBI

The global prevalence of OBI has not been clarified yet because of several practical issues. Firstly, for general population or subjects without any evidence of liver disease, hepatitis B serology is not surveyed routinely. Secondly, for patients with known but resolved HBV infection, serum HBV DNA is almost not tested. Thirdly,

the HBV DNA level in serum of patients with OBI is usually too low to be detected by standard commercial assays. Previous studies have shown that the HBV DNA levels in patients with OBI were typically less than 10–20 IU/mL (Morales-Romero et al. 2014; Yuen et al. 2011). Finally, measuring HBV DNA in the liver tissues may help detection of OBI; however, the invasive nature of liver biopsy makes it an unpopular approach (Yuen et al. 2008, 2010, 2011; Song et al. 2009; Bhatti et al. 2007; Werle-Lapostolle et al. 2004; Reesink et al. 2008; Georgiadou et al. 2004; Fang et al. 2009; Minuk et al. 2005; Kim et al. 2007; Svicher et al. 2012).

5 Prevalence of OBI in the East

Chronic HBV infection is the leading cause of chronic hepatitis, cirrhosis, and hepatocellular carcinoma (HCC) in the Asian-Pacific region (Chen 2000; Merican et al. 2000). Globally, more than 70% of HBV infections occur in the Asian-Pacific region.

The prevalence of persistent as well as past infection is high in South and Southeast Asia (Alter 2003). Mongolia is also highly endemic for HBV infection (Alter 2003). In these areas, more than 8% of the general population is positive for HBsAg, 40 to 90% of the adult population has serological evidence of previous HBV infection, and 4 to 25% of the HBsAg (−) and anti-HBc (+) subjects have detectable serum HBV DNA (Minuk et al. 2005; Lai et al. 1989; Wang et al. 1991; Iizuka et al. 1992; Nagaraju et al. 1994). In these highly endemic areas, the majority of infections occur perinatally or in early childhood, a high proportion of the infected adults have late chronic HBV with undetectable HBsAg; this phenomenon may account for the high rate of OBI in anti-HBc-positive populations in these areas.

In areas of Asia with an intermediate prevalence of HBV infection including Middle East countries, India, South Asia, and Korea, the prevalence of HBsAg ranges from 2 to 7%. About 16 to 55% of the population has serologic evidence of past HBV infection.

In well-developed countries of the Asia-Pacific area including Australia and Japan, the prevalence of chronic HBV infection is usually less than 1%. Only 4 to 15% of the adult population has evidence of HBV infection rate (Alter 2003). Among these low prevalence countries, HBV DNA could be found in less than 5% of the HBsAg (−), anti-HBc (+) blood units (Allain et al. 1999; Kleinman et al. 2003).

6 Prevalence of OBI in the West

The prevalence of OBI also varies in different geographical areas in the west. Recently, a systematic review and meta-analysis were conducted in Western Europe and in Northern America (Pisaturo et al. 2020). Interestingly, their data showed that the prevalence of OBI was high in HBsAg-negative patients. Besides, the presence of OBI was associated with anti-HBc positivity (Pisaturo et al. 2020). Totally, 34% of the general population had evidence of OBI; 28% (95% CI, 12–48%) in 329

subjects without chronic liver disease, and 35% in 2400 patients with chronic liver disease. Subgroup analysis further revealed that the prevalence of OBI was 51% and 19% among the 823 anti-HBc-positive subjects and the 1041 anti-HBc-negative subjects, respectively.

7 Prevalence of OBI in Different Clinical Situations

There is ample evidence in cross-sectional studies demonstrating the persistence of HBV DNA in patients with HBsAg-negative HBV infections. Overall, serum HBV DNA was documented in 5 to 55% of HBsAg-negative chronic hepatitis patients with chronic hepatitis (Torbenson and Thomas 2002; Brechot et al. 2001; Hu 2002). For patients with HCC, OBI was found in 14 to 100% of anti-HBc-only positive patients; and OBI was found in 8 to 87% of the seronegative patients without any markers of HBV infection (Paterlini et al. 1990; Thiers et al. 1993; Fukuda et al. 1996; Shintani et al. 2000).

For patients with fulminant hepatitis, OBI is documented in around 10% of HBsAg-negative patients. OBI can also be observed in apparently healthy individuals with normal liver function tests (Wang et al. 1991; Marusawa et al. 2000; Shih et al. 1990; Hennig et al. 2002). Again, the rate of HBV DNA is significantly higher in healthy individuals with anti-HBc alone. Allain et al. reported that for anti-HBc-positive subjects, the average HBV DNA detection rates were 7 and 13% among these subjects with versus without anti-HBs, respectively. In blood donors, the rates of OBI ranged from 0 to 17% (Allain 2004).

In the west, a recent review demonstrated that the prevalence of OBI ranges from 4 to 38% in patients with cryptogenic cirrhosis or advanced liver fibrosis (Squadrito et al. 2013; Hou et al. 2001; Chan et al. 2002), is about 45% in patients with a history of exposure to blood product, is 52% in chronic hepatitis C patients, ranges from 0% to 45% in patients infected with HIV, ranges from 0% to 22.7% in blood donors (Kishk et al. 2015; Sofian et al. 2010) and ranges from 0% to 54% patients receiving hemodialysis (Minuk et al. 2004).

8 Clinical Implications

8.1 Transmission of HBV through OBI

Any product containing full HBV viral particles is considered to be potentially infectious. According to a chimpanzee study, HBV DNA of only 10 copies can already achieve the minimum 50% infectious dose of HBV (Komiya et al. 2008). OBI donors, although usually having very low HBV viremia, may thus still transmit the HBV to susceptible individuals in the setting of blood donation. Several confounding factors in human situations further influence the transmission of HBV from OBI subjects, including the anti-HBs status of both the donors and the recipients, the kind and the volume of the blood products being transfused to the

recipients, and the immunological status of the recipients (Raimondo et al. 2013; Mosley et al. 1995; Satake et al. 2007).

Transmission by blood components negative for HBsAg can occur either in the acute phase of infection during the seronegative window period or during chronic stages of infection (i.e., OBI). Because of limitations in previous blood screening practices, OBI is a risky but overlooked source of HBV transmission.

The prevalence of OBI among blood donors varies globally. For example, in Egypt, the rate of OBI can be as high as 22.7% (Kishk et al. 2015). In Iran, none was found to have OBI (Sofian et al. 2010). Screening 14,937 young blood donors born between 1992 and 1997 in China (in the era of universal HBV vaccination) documented that 10 (0.067%) of these donors had detectable serum HBV DNA, indicating the presence of OBI (Tang et al. 2018).

Regarding the screening for HBV infection in blood donors, it would be useful to assess the relative contribution of two potential sources of transfusion-transmitted HBV infection from HBsAg-negative donations. Anti-HBc screening can eliminate the residual risk of occult HBV transmission by transfusion in low-endemic areas. On the contrary, nucleic acid amplification test (NAT) would be effective in the screening of blood donors for OBI in highly endemic countries. However, the cost-effectiveness of different blood screening strategies in different countries needs to be investigated further (Liu et al. 2006).

Although there are already many human studies examining the transmissibility rate of HBV from blood donors with OBI, most of these studies are retrospective in nature. We could not trace back the potential donors or the infectious origin. There are several studies performed to determine the HBV transmission rate from OBI donors. It was found that the transmission rate was low, at around 1–3% (Yuen et al. 2011; Mosley et al. 1995; Candotti and Allain 2009). The risk was furtherly reduced if the donor serum was anti-HBs positive (Mosley et al. 1995). There are studies showing that HBV transmission is possible from anti-HBc positive donors (Hoofnagle et al. 1978; Lander et al. 1978; Koziol et al. 1986). The transmissible rate is around 2.4–3.0% (Lai and Yuen 2009).

From another aspect, although OBI is transmissible through blood transfusion to HBV-naïve recipients, its impact on recipients with prevalent HBV infection in HBV hyperendemic areas is unclear. To address this issue, we consecutively collected HBV-naïve recipients indicated by anti-HBc-negative, with normal ALT, and followed their HBV DNA and serologic markers before and after transfusion in Taiwan (Liu et al. 2006). Among 4448 blood unit recipients, we collected 467 (10.5%) anti-HBc-negative recipients and completed the posttransfusion follow-up in 327 recipients. We identified 5 (1.5%) recipients who developed hepatitis B viremia 1 week after transfusion. Three were children with subclinical acute infection (anti-HBs positive from birth HBV vaccination in all 3 children), one had transient transfusion-transmitted HBV without seroconversion to anti-HBc and one had OBI. Our findings suggested that OBI was transmissible by transfusion in HBV endemic areas. The incidence of posttransfusion acute HBV infection was 0.9% (100 per million units) in naïve recipients in Taiwan, approximately 40-fold higher than in developed countries. Moreover, some vaccinated children with anti-HBs

were still susceptible to HBV infection. Our findings indicated that sensitive screening assays for OBI such as NAT should be considered in endemic areas.

We further conducted a look-back study to determine the clinical significance of OBI-positive blood transfusion in Taiwan (Su et al. 2011). In 2006, we identified 12 occult HBV blood donors from 10,824 repository samples by using NAT. The 74 corresponding recipients were further identified. Among the 74 recipients, 18 were alive and 12 were called back to our clinic. However, only 24 recipients had available posttransfusion serological profiles; none was seroconverted to be HBsAg positive. One recipient had an identical sub-genomic sequence of HBV surface gene (384 nucleotides) to his donor. Our findings suggested that in HBV hyperendemic areas, OBI was transmissible. However, the risk of transfusion-transmitted HBV infection is low.

9 HCC Development

It is widely debated whether OBI may accelerate the disease progression toward cirrhosis and the development of HCC in patients with other chronic liver diseases. While many studies have shown a significant association between OBI and HCC in patients with chronic hepatitis C (Squadrito et al. 2013; Shetty et al. 2008; Wang et al. 2018), other studies found no association (Lok et al. 2011; Chen et al. 2017). It is believed that the OBI-related HCC risk, if exists, is very limited although OBI potentially maintains the pro-oncogenic properties attributed to the HBV infection (Saitta et al. 2015). More large cohort studies are needed to address the issue.

10 HBV Reactivation after Immunosuppressant

HBV reactivation is defined as a sudden surge of viral load, which is attributed to inadequate host immune control over HBV replication and is followed by varying degrees of liver necroinflammation or even liver decompensation. Although spontaneous HBV reactivation is not rare in HBsAg-positive patients with a low viral load, (Tseng et al. 2013), HBV reactivation occurs more frequently in the HBsAg-positive CHB patients undergoing chemotherapeutic treatment and immunosuppressive therapy, such as stroid-containing regimen (Cheng et al. 2003). A substantial risk of HBV reactivation develops after host immune response is suppressed and prophylactic antiviral treatment is recommended in this clinical circumstance.

In patients with resolved HBV infection, HBV reactivation is characterized by either the reappearance of HBsAg, the reappearance of HBV DNA with a record of undetectable HBV DNA, or a tenfold increase of HBV DNA with previously detectable serum HBV DNA. HBV reactivation rarely occurs in patients with resolved HBV infection after traditional chemotherapy. However, it has become a more serious problem with the increasing use of monoclonal antibodies with potent immunosuppressive effects for autoimmune diseases and hematological malignancies (Raimondo et al. 2019; Yeo et al. 2009).

It is first shown that approximately 24% of anti-HBc-positive subjects receiving cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP) plus anti-CD20 (rituximab) experienced HBV reactivation resulting in one death (Yeo et al. 2009). On the other hand, there is no HBV reactivation in anti-HBc-positive subjects if they received rituximab-free treatment regime. It strongly suggests that rituximab, a B cell-depleting agent, significantly increases the risk of HBV reactivation in patients with resolved HBV infection.

This issue is further studied in detail by other prospective studies. Of the 63 HBsAg-negative, anti-HBc-positive subjects (all with undetectable serum HBV DNA) receiving R-CHOP, 42% of subjects develop HBV reactivation (Seto et al. 2014). It is also found that the rate of HBV reactivation is lower in anti-HBs-positive subjects compared with anti-HBs-negative subjects (34% vs. 68% respectively, $p = 0.012$). Furthermore, the result from a randomized control study shows that entecavir prophylaxis minimizes the risk of HBV reactivation in patients with resolved HBV infection after R-CHOP (HBsAg seroreversion rates were 16.3% vs. 0%) (Huang et al. 2013).

Two important factors determine the risk of HBV reactivation in resolved HBV patients after R-CHOP. One is serum levels of anti-HBs, which reflects the host humoral immune response. A meta-analysis has demonstrated the protective value of detectable anti-HBs levels (Paul et al. 2017). The other is the presence of residual replicative cccDNA in the liver. Several biomarkers indicating residual replicative templates have been explored to predict the risk of HBV reactivation after R-CHOP treatment in patients with resolved HBV infection. The first biomarker is the detectable HBV DNA in serum, which is commonly used to define OBI. Although not all the data support its role in predicting HBV reactivation (Yang et al. 2018; Huang et al. 2013; Seto et al. 2014), the data from a large cohort study enrolling 266 Asian patients showed that patients with detectable HBV DNA level (2.2% of the overall cohort) are associated with HBV reactivation (Kusumoto et al. 2015). The second potential biomarker is hepatitis B core-related antigen (HBcrAg), which is a viral protein translated from cccDNA. Of the 124 patients receiving either rituximab-containing chemotherapy or allogeneic hematopoietic stem cell transplantation from a prospective study, they found that detectable HBcrAg level at baseline (17.7% of the overall cohort) is associated with higher risk of HBV reactivation (Seto et al. 2016). The third biomarker is quantitative anti-HBc, which has been shown to be positively associated with cccDNA levels in patients with resolved HBV infection (Caviglia et al. 2018). Of 197 patients receiving R-CHOP treatment from a prospective study, a higher anti-HBc level at baseline (≥6.41 IU/ml, 35.9% of the overall cohort) is associated with increased risk of HBV reactivation (Yang et al. 2018). The fourth biomarker is ultra-high sensitivity HBsAg assay, which detects the HBsAg contained in the immune complex and has a lower detection limit than conventional HBsAg assay (0.0005 IU/ml vs. 0.05 IU/mL) (Kusumoto et al. 2020). Of the 252 patients with HBsAg <0.05 IU/mL, 4 patients had detectable HBsAg by ultra-high sensitivity HBsAg assay and all of them had HBV reactivation. Although all these biomarkers do not directly detect the intrahepatic cccDNA, which indicates the presence of OBI, these surrogate biomarkers indicate the presence of residual cccDNA and help clarify the role of OBI in inducing HBV reactivation after R-CHOP.

HBV reactivation is also an important issue for patients with hematological malignancy because there is a high degree of bone marrow suppression by intense immunosuppressive therapy, especially for those receiving hematopoietic stem cell transplantation (HSCT). The rate of HBV reactivation in HSCT patients with resolved HBV infection is in a range of 2.4 and 43% as reported by different studies, which may be influenced by the definition of HBV reactivation (Vigano et al. 2011; Hammond et al. 2009; Seto et al. 2017; Chen et al. 2018). A prospective study including 62 HSCT patients shows that the HBV reactivation is as high as 40% within 2 years of follow-up but HBsAg seroreversion occurred only in one patient (7.7%) (Seto et al. 2016).

HBV reactivation has also been reported in patients with resolved HBV infection after biologic therapy. According to a large-scale study including 468 Asian HBsAg-negative and anti-HBc-positive patients, the use of antitumor necrosis factor was associated with the HBV reactivation rate of 1.7% (Lee et al. 2013), in contrast to the zero risk reported in Western countries (Pauly et al. 2018; Barone et al. 2015). To be noted, patients with rheumatology disease usually receive different kinds of biological therapy, and it is sometimes difficult to attribute the risk of HBV reactivation to a specific drug (Chen et al. 2020). The current data suggest the risk of HBV reactivation from patients with resolved HBV infection is limited after biological therapy except using B cell-depleting agent.

Prophylactic antiviral agents are recommended for chronic hepatitis B patients with risk of HBV reactivation >10% after chemotherapy or immunosuppressant treatment (Reddy et al. 2015). For OBI subjects, this practice is also widely adopted for those with detectable HBV DNA. A controversy, however, exists in HBsAg-negative, anti-HBc-positive patients with undetectable HBV DNA. Currently, prophylactic antiviral treatment is recommended for all the patients with resolved HBV infection receiving rituximab-containing chemotherapy. However, there is a high prevalence rate of resolved HBV infection in Asia. A cost-effective alternative is to identify the high-risk patients (>10% of reactivation rate) for prophylactic antiviral treatment while arranging a close observation for the rest of the patients. The risk stratification needs more data from different viral and host biomarker research. Several studies have shown that monitoring of HBV DNA or ultra-high sensitive HBsAg monthly for prompt antiviral treatment when HBV DNA or HBsAg detected is effective to avoid HBV-associated hepatitis (Kusumoto et al. 2020; Kusumoto et al. 2015). At present, there are no studies to show the best monitoring strategy and more studies are needed to optimize the management.

11 Reactivation of HBV in Chronic Hepatitis C Patients Receiving DAA Therapy

Reactivation of HBV activity has been an important clinical concern in HCV/HBV coinfected patients receiving anti-HCV therapy in the era of pegylated interferon plus ribavirin combination therapy (Liu et al. 2009).

After the introduction of direct-acting antiviral (DAA) for the treatment of chronic hepatitis C, the awareness of HBV reactivation was further increased.

During 108 weeks after DAA treatment, HBV virologic reactivation occurred in 73% of patients (81/111) (Liu et al. 2017). Clinical reactivation occurred in 9% of participants (10/111). Our data clearly indicated that among HCV/HBV coinfected patients treated with DAAs for HCV, HBV virologic reactivation occurred commonly and should be monitored.

In contrast to overt HBV/HCV coinfection, patients with chronic hepatitis C and coexisting OBI have a minimal risk of HBV reactivation after the start of DAA therapy in previous studies and meta-analysis (Liu et al. 2017; Pisaturo et al. 2019). Per regional guidelines, only serum ALT monitoring is recommended for HCV/OBI coinfected patients; and serum HBV DNA or HBsAg testing is reserved for those patients experiencing serum ALT elevation of unknown etiology.

12 Conclusion

In summary, OBI is now a disease entity with increasing attention in various aspects of liver diseases. The diagnosis of OBI could be affected by the different sensitivity of HBsAg and HBV DNA assays. The prevalence is yet to be studied comprehensively in different population across the world. OBI patients usually have low viral load thus may not need antiviral therapy in general conditions. There is a risk of HBV transmission through blood transfusion, which has been minimized by the application of NAT screening for blood products. HBV reactivation from OBI is being increasingly recognized after the introduction of potent B cell-depleting therapy. Although prophylactic antiviral therapy minimizes the risk of HBV reactivation, the best strategy to prevent HBV reactivation in these patients remains to be defined (Fig. 17.1).

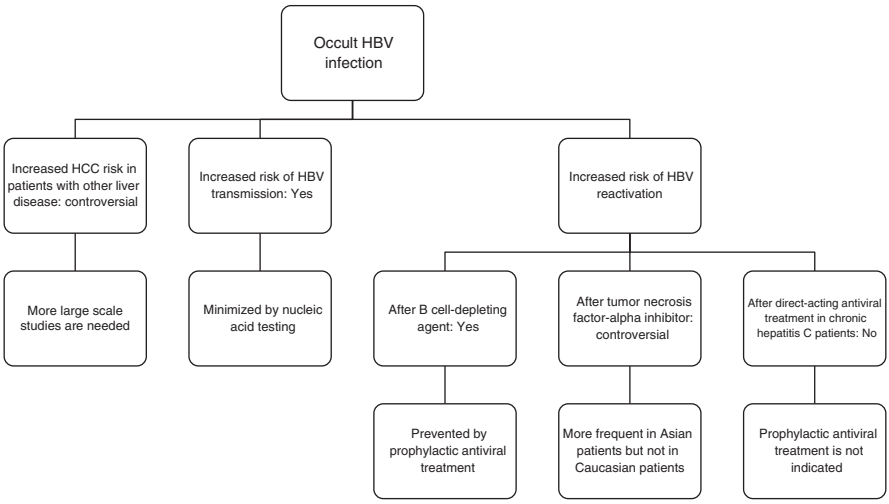

Fig. 17.1 Clinical significance and management of occult hepatitis B virus infection (OBI)

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