Occult hepatitis B virus infection: risk for a blood supply, but how about individuals' health?

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Summary

The implementation of effective blood donation screening for hepatitis B virus (HBV) anti-core antibodies with highly sensitive molecular HBV DNA detection in low-endemic countries like the United Kingdom has improved blood safety. However, the linkage to care and management for blood donors with occult HBV infection (OBI) is a complex dilemma involving virological, clinical, methodological, and social issues. Limited evidence suggests that OBI may accelerate the progression of liver disease and cancer. The need for a specialist referral for donors identified with OBI carries mixed opinions from blood establishments, hepatologists, and public health. Following extensive multidisciplinary discussions, experts agree upon a need for clear messaging for donors and to consider the oncogenic implications of OBI. Proposals for future studies are identified, and the applicability of the recommendations in low-resource, high-endemic regions is considered, as well as the inclusion of OBI in global hepatitis elimination targets.

Keywords: Hepatitis B; Blood donors; Liver diseases; Referral and consultation; Consensus

Introduction

Individuals chronically infected with the hepatitis B virus (HBV) are at increased risk of developing cirrhosis, and HBV infection is the leading cause of hepatocellular carcinoma (HCC) worldwide.[1] Chronic HBV infection is associated with significant morbidity and mortality globally, with 1,100,000 deaths per year globally due to HBV-related sequelae.[2] In England in 2022, there were around 270,000 individuals (0·6% of the population) living with hepatitis B.[3]

Common biomarkers are used to ascertain HBV infectious status. HBV surface antigen (HBsAg) and HBV DNA in plasma indicate the generation of viral proteins and/or active viral replication, whilst antibodies against the HBV core antigen (anti-HBc) indicate a past or present infection.[4] Immunity to HBV infection from immunisation is associated with high levels of antibodies to the HBV surface antigen. HBV e-antigen and antibodies to the e-antigen are essential biomarkers in the clinical management of infected individuals. Most HBV screening programmes utilise testing for HBsAg as a marker of chronic HBV infection, but screening of immunocompromised patients and blood donors also includes anti-HBc as a marker of exposure to HBV

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infection (Table 1). This is because individuals who are HBsAg-negative but anti-HBc positive are recognised as possible carriers of occult HBV infection (OBI). OBI is formally defined as the presence of replication-competent covalently closed circular (ccc)DNA in the liver regardless of HBV DNA presence in the blood, but negative in standard serological tests for HBsAg.[5] When detectable, viral loads in the blood of individuals with OBI are usually very low (less than 200 IU/mL).

HBV, as a blood-borne virus, is transmitted through contact with infected blood or bodily fluids; immunisation of at-risk individuals and screening to prevent transmission of HBV are key preventative measures to limit the spread of HBV (Table 1). Universal antenatal screening of pregnant persons for HBsAg at 16 weeks of pregnancy[6] has been shown to almost completely eliminate the risk of mother-to-child transmission of HBV in England by providing adequate treatment for the infected mothers and prompt post-exposure prophylaxis to their babies,[7] whereas screening of blood donations for HBsAg, HBV DNA and anti-HBc aims to prevent HBV transmission via blood transfusion from donors with chronic and occult HBV infection.[8] Haemodialysis patients are also screened for HBsAg so that the dialysis of HBV-infected and non-infected patients can be segregated to prevent the transmission of HBV.[9] HBV reactivation has also been well-documented in immunocompromised individuals who have evidence of past HBV infection and thus potentially have replication-competent HBV DNA in the liver; screening patients for anti-HBc before commencing immunosuppression aims to identify those at risk of reactivation and guide their prophylactic antiviral treatment.[10]

HBV screening during pregnancy is part of routine antenatal care; the follow-up of mothers with chronic HBsAg-positive HBV infection is organised by specialist midwives and supported by doctors from different medical specialities. Both screening of haemodialysis and immunocompromised patients for HBV is performed in hospital settings, where the patients are already linked to secondary care. In contrast, blood donation screening of healthy volunteers is not done in a hospital setting; hence, linkage to care is more complex. In the United Kingdom (UK), blood donors with chronic or acute HBV infection are contacted for post-test discussion by a trained nurse or medical doctor, usually via telephone, and they are subsequently referred for specialist care via their general practitioners (GPs). However, the management of individuals with OBI presents a complex dilemma that requires attention but has not been previously addressed in this context. Our viewpoint is based upon extensive discussions over a decade involving the UK's leading experts in hepatology, viral hepatitis, clinical virology, transfusion microbiology and public health.

Blood donation screening for HBV in the UK

Anti-HBc was introduced into the blood donation screening programme in the UK in 2022 to defer anti-HBc positive donors and eliminate the risk of transfusion-transmitted HBV infection associated with donors with OBI.[11,12] OBI donors have undetectable levels of HBsAg in their blood but are anti-HBc positive; active infection is revealed through often transient, low-level detection of HBV DNA in their plasma.[11] The minimum infectious dose of OBI donor plasma by transfusion has been shown to be 3 IU.[13] Seven cases of HBV transmission from six donors with OBI were described in the UK between 2012 and 2022, some with severe medical consequences.[14] Further modelling predicted that at least 13 potentially infectious donations from donors with OBI would be missed by the relatively insensitive pooled nucleic acid testing (NAT) currently used by UK blood services.[8,15] This exceeded the risk of non-detection due to acute HBV infection by eight-fold. These predictions were borne out during the first year of partial anti-HBc screening, where from the 3359 anti-HBc positive blood donors identified, eight donors had low levels of HBV DNA detected in their plasma by individual NAT. An international study found that HBV DNA detectability was 0.7% in over 10 million anti-HBc

Screening group/programme	Marker	Timing	Aim of prevention	Guideline
People at risk of hepatitis B infection	HBsAg	Upon identification of risk factors	Person-to-person HBV transmission	European Association for the Study of the Liver
Antenatal Screening	HBsAg	16 weeks of pregnancy	Mother-to-baby transmission of HBV	UK National Screening Committee
Blood donation screening	HBsAg, HBV DNA and anti-HBc	Every blood donation for HBsAg and HBV DNA; new donors only for anti-HBc	HBV transmission via blood transfusion	Advisory Committee on the Safety of Blood, Tissues and Organs
Dialysis screening	HBsAg	Haemodialysis patients in 3-month intervals	HBV transmission in haemodialysis units	The UK Kidney Association
Screening of patients undergoing immunosuppressive therapy	HBsAg and anti-HBc	Before commencing immunosuppression	HBV reactivation	European Association for the Study of the Liver

Anti-HBc, hepatitis B virus anti-core antibodies; HBV, hepatitis B virus; HBsAg, hepatitis B virus surface antigen; UK, United Kingdom.

Table 1: **Summary of screening strategies and programmes utilised in the United Kingdom to prevent transmission and reactivation of HBV in various cohorts.**

positive blood donors from low-endemic countries.[16] It is noted that whilst health economic evaluations found that anti-HBc screening was more economical than individual NAT screening for the UK,[8] anti-HBc screening would be unfeasible in high-endemic countries due to the large number of individuals exposed to HBV infection.[16]

Occult HBV infection

OBI is a challenging clinical entity to diagnose. No established markers predict the presence of cccDNA in the liver independently of the detection of circulating HBV DNA in plasma; potential biomarkers of cccDNA replicative status, such as circulating HBV RNA, have been suggested.[17] Laboratory diagnosis of OBI based on plasma samples alone is thus somewhat dependent on the (in)sensitivity of the serological assay used for HBsAg detection and, in the absence of a liver biopsy sample, the sensitivity of the assays used to detect HBV DNA in plasma. In addition, the tendency of some OBI carriers to have HBV DNA levels that fluctuate above and below the lower limit of laboratory detection introduces both frequency of testing and an element of chance into the likelihood of identifying OBI. Assay-dependence of OBI diagnosis was indeed illustrated by our application of an ultrasensitive PCR method to screen anti-HBc positive donors,[12] which achieved a four-fold increase in HBV DNA detection rate compared to the HBV NAT assay used for blood donation screening. Differences in the sensitivities of HBV DNA tests used for blood donation screening and standard clinical diagnoses could lead to misunderstanding of HBV infection status and create additional confusion and worry for individuals with OBI.

OBI may result from various phases of the natural history of HBV infection. Firstly, a prolonged resolution stage of acute HBV infections will mimic the plasma markers of OBI.[5] Alternatively, false-negative HBsAg results that may incorrectly identify OBI may arise from carriers of HBV strains with mutations in the antigenic 'a' determinant of the HBsAg gene that escapes detection by many currently available HBsAg assays or with mutations that prevent HBsAg secretion.[17] Cases of seronegative OBI have also been described globally, where individuals may have lost hepatitis B antibodies or may not have produced antibodies throughout their HBV infection.[5] Further, studies have shown that in Chinese blood donors, around 9.5% of OBI carriers were anti-HBc negative but anti-HBs positive with a high 72% vaccination rate[18]; this serological profile could lead to further diagnostic difficulties. However, no anti-HBc negative OBI cases have been documented in the United Kingdom. The typical serological profile of OBI is where HBsAg becomes undetectable following decades of HBsAg-positive HBV infection corresponding to the last phase in the natural history of HBV infection.[10]

Both prospective and retrospective studies have demonstrated that HBV reactivation occurred in a pooled 6·5% cohort of individuals with potential OBI (HBsAg-negative and anti-HBc-positive) receiving immunosuppressive therapy.[19] During immunosuppression, immune control of HBV is lost, leading to the resumption of viral replication, often at high levels. This can lead to fulminant hepatitis,[20] usually occurring after reduction or cessation of immunosuppression, as a reconstituted immune system acts against HBV-infected hepatocytes. For this reason, the European Association for the Study of Liver Disease guidelines recommend prophylactic therapy in HBsAg-negative but anti-HBc-positive patients receiving those immunosuppressive regimens with the greatest risk, such as rituximab.[10]

OBI may sustain a prolonged state of liver inflammation, as suggested by a prospective study in Japan that showed the presence of cccDNA in all patients a decade after clinical recovery from acute self-limiting HBV infection and liver fibrosis and mild inflammation was detected in 89% of patients.[21] OBI seems to accelerate the progression of chronic liver disease and liver fibrosis in hepatitis C virus (HCV) co-infection,[22] where multiple studies have shown that the incidence and risk of HCC in HCV-infected patients with OBI was significantly greater than in HCV-infected patients without OBI.[22–24] However, one study in the USA found OBI in 10.7% of HBsAg-negative patients with advanced chronic HCV and HCC compared to 23.6% of similar patients but without HCC.[25] Data on other liver disease aetiologies is limited, with a recent study finding a 12.8% prevalence of OBI in obese patients undergoing bariatric surgery, suggesting OBI is a major risk factor for metabolic dysfunction-associated steatotic liver disease.[26]

HBV is a primary aetiological agent of HCC worldwide,[27] with a well-established causal relationship between chronic HBsAg-positive infection and HCC. However, the association between OBI and HCC is less well-defined and has only been confirmed by retrospective studies, with no prospective studies. Retrospective studies found a high proportion (>60%) of Asian and European patients with cryptogenic HCC who had OBI.[28–30] In sub-Saharan Africa, where the HBV burden is high, a recent study found a high rate of anti-HBc positivity (16/36; 44%) and HBV DNA positivity (2/36; 6%, limit of detection 15 IU/mL) in HBsAg-negative patients with chronic liver disease and no identifiable cause.[31] Compared to HBsAg-positive chronic HBV infection, it is plausible that there is a lower oncogenic risk profile for individuals with OBI, considering the typically lower cccDNA levels and transcriptional activity, along with lower expression of viral proteins and necroinflammation that modulate hepatocarcinogenesis.

A prospective study in Hong Kong in HBV-infected patients with HBsAg seroclearance showed that 2·34% (7/298) developed HCC over a median follow-up of nine years, where all seven patients were over 50 years of age and seroclearance below the age of 50 was associated with a significantly lower risk of fibrosis and HCC.[32] Another Japanese prospective study with 82 cryptogenic cirrhotic patients showed that HCC incidence was 100% with and 17·6% without OBI at ten years (p = 0.008; hazard ratio 8·25).[33] Indeed, a body of literature suggests that OBI maintains the pro-oncogenic properties of HBsAg-positive HBV infection, with the ability to integrate HBV DNA into the host genome and persisting levels of pro-oncogenic X and pre-S/S viral proteins.[34] There have been reports of HBV integration in up to 75% of HCC cases with undetectable HBsAg levels,[28,35] a comparable prevalence to that in HBsAg-positive HCC cases.[36] However, despite this evidence, whether OBI could mediate liver damage remains a significant and debated topic, but an issue that clinicians should be mindful of in at-risk patient groups.

Follow-up of blood donors with occult HBV infection

Management in England and Wales

Deferred donors in England and Wales diagnosed with OBI (anti-HBc positive, HBsAg-negative, HBV DNA positive) receive a letter accompanied by an information leaflet and question and answer sheet. OBI donors are invited to join a discussion via telephone, usually conducted by a trained nurse, to identify the most likely risk factor for their HBV infection and the importance of precautionary specialist referral. Donors are also informed that their HBV serological information will be useful for their treating physician should they become immunosuppressed. GPs are then notified with donors' consent and advised to refer the donors for hepatology review. The GP is then asked to confirm that the referral has taken place. The specialist referral aims to ensure no evidence of liver disease or cirrhosis; donors without evidence of liver disease can be reassured that their risk of future disease is very low. This follow-up strategy of communicating with the donor and/or their GP and referral to a specialist is also utilised by other blood establishments worldwide,[16] noting that the type of healthcare model could influence referral pathways.

Management in Scotland

Deferred OBI donors with HBV DNA levels of at least 10 IU/mL are invited to contact the donor medical team to discuss sources of HBV infection and potential health implications and gain consent for direct specialist referral. The donor's GP is then notified of the discussion and referral. OBI donors with HBV DNA levels less than 10 IU/mL are managed as donors with cleared infection as advised by the Scottish Viral Hepatology Clinical Network, with a letter and accompanying information leaflet. They are also provided with a separate letter for GP notification and can contact the donor medical team to discuss their results further. Routine specialist referral and further clinical action are not advised for this cohort on the basis that HBV DNA levels less than 10 IU/mL are not detectable with assays used in hospital laboratories.

Discussion

There is currently no professional consensus on the need to follow up with OBI donors. From the point of view of the donors' blood services and GPs, this action provides the optimal reassurance to the donor. However, from a hepatology view, the clinical relevance of OBI and the need for follow-up is questioned since overdiagnosis consumes health resources and may lead to anxiety. An HBsAg-negative, anti-HBc-positive patient would not routinely undergo HBV DNA testing nor be referred to hepatology. It can be considered illogical to do so solely due to the test occurring in the blood donation setting, as current evidence does not suggest this to be a proportionate response. Indeed, given the general good health of blood donors, such a response is even less likely to meet an acceptable threshold for benefit and may lead to unwarranted impacts on patients, including psychological and financial (direct and indirect, depending on the healthcare system). From a public health perspective, there is a need for clear messaging for these donors so that the notifications and any required actions are clear for the donor. Further, the importance of offering equal opportunities and the sensible use of limited resources based on risk are stressed.

It is agreed that there should be clear and consistent messaging provided for blood donors with OBI during diagnosis and follow-up, and education for the staff involved in follow-up is needed to ensure the reasons behind the referral are well understood, combined with clear guidelines and structure for healthcare providers regarding follow-up and referral. However, there may currently be a mixed message between the blood service and the hepatologist; donors cannot donate due to their infectious risk, but the infection risk is not a concern for hepatologists and the risk to individuals' health is also considered minimal. Since OBI is not without its consequences, OBI carriers who have other risk factors that increase their risk of developing liver damage should at least be given some advice. The potentially sinister connotations of 'occult' also present a problem, where the terminology for the condition in patient-facing resources may require review.

The practical and ethical implications of informing individuals that they have a potentially increased risk of cancer but with no actionable recommendations is a challenging conversation where clinicians and patients

may have differing views on the matter. Whilst transparency is important for individuals' autonomy, the ethical implications may be affected by differing healthcare systems. Individuals in low-to-middle-income countries lacking universal healthcare could be psychosocially affected by the information provided but are restricted by access and affordability to follow-up care, which may include costly diagnostic tests and monitoring strategies. Being asymptomatic, individuals may not perceive the need for follow-up care. Additionally, high-endemic countries may prioritise limited resources on public health interventions rather than individual risk communication and follow-up. In certain societies, the disclosure of an increased risk of cancer due to HBV may also be heavily stigmatising and worsen the psychosocial impact on the individual.

Further, the use of sensitive HBV DNA assays in blood donor screening to identify HBV-infected donors with very low viral loads highlights the existence of a potentially neglected reservoir of HBV infection in the general population, particularly when anti-HBc positive individuals may harbour replication-competent HBV DNA in their livers despite the absence of circulating HBV DNA. Additionally, patients achieving a 'functional cure' following currently available antiviral treatment (defined as sustained undetectability of HBsAg (<0.05 IU/mL) and an undetectable or extremely low level of HBV DNA (<10 IU/mL)[37]) may still have very low viral loads and potentially contribute to the growing pool of OBI carriers; limited evidence also suggests that many patients who achieve 'functional cure' also have low and persisting levels of replication-competent DNA in their livers.[32] This combined pool of OBI carriers and the ambiguity of 'functional cure' may affect the World Health Organization (WHO)'s goals to eliminate hepatitis B by 2030.[2] Future therapies targeting the intrahepatic HBV DNA would be extremely beneficial in achieving a full HBV cure.

Future directions

Firstly, reviewing the information and advice provided to donors is vital, especially surrounding the messaging on what having OBI entails for the individual. Communication with donors should be clear and culturally sensitive regarding risk notification and guidance to accessible resources. The involvement of donors carrying OBI in research would enable a better understanding of the needs and expectations of donors who receive an OBI diagnosis. Such research would give insight into how an OBI diagnosis affects the psychological well-being of donors and whether current support mechanisms are adequate. It is expected that some donors with OBI may prefer to have the opportunity to be followed up, even though the rationale for doing so might be unclear. Although studies, mainly in Asia and Africa, have observed OBI in vaccinated newborns from HBsAg-positive mothers,[5] there exists uncertainty surrounding the infectivity of individuals with OBI and the precautions that the individual and their contacts may take.

There is a need to consider the oncogenic impact of OBI. Extensive and methodologically appropriate studies are necessary to investigate the real-world prevalence of OBI in cohorts of patients with chronic liver disease, especially those of cryptogenic and non-HCV-related origins. Follow-up data regarding the prognosis of OBI individuals is also needed, as well as establishing a longitudinal cohort study to ascertain the presence or absence of liver disease in OBI blood donors. The risk of liver-related complications may also vary between different origins of OBI, e.g., occult infection following decades of HBsAg-positive infection compared to OBI following acute HBV infection or seronegative OBI individuals. Such studies may provide the necessary data to delineate individuals with OBI at risk of HCC through viral and host factors. However, blood donors are pre-selected for low frequencies of co-morbidities and low risk of infectious disease acquisition, meaning that such studies would require several decades of follow-up. The unrepresentative nature of donors is highlighted by the human T-lymphotropic virus (HTLV) registry study showing that blood donors with asymptomatic HTLV infection identified via blood donation were invariably asymptomatic and showed a greatly reduced risk of developing HTLV-associated myelopathy or adult T-cell leukaemia/lymphoma compared to non-donor cohorts.[11] Nonetheless, creating a global cohort of OBI donors with standardised aggregated data collection on their clinical outcomes, including complications of liver disease, would provide the necessary evidence to guide future policy for the follow-up of an OBI carrier, such as whether they should be assessed with liver function tests and an evaluation of hepatic fibrosis and steatosis.

Search strategy and selection criteria

Consensus discussions took place via an in-person meeting followed by a virtual Microsoft Teams meeting, with notes circulated before and after meetings to allow experts to review and contribute. To support the discussions, existing literature was searched via PubMed for full-length articles from Jan 1, 2000, to Oct 1, 2024, using the search term "hepatitis B" combined with the terms "occult," "cirrhosis," "hepatocellular carcinoma," and "blood donation." Full texts of relevant titles were reviewed for relevance and importance of contributions to the topics presented in this viewpoint. Further seminal publications were selected from the identified articles' reference lists. There was no geographical restriction, noting a lack of studies from high-endemic regions such as sub-Saharan Africa.

OBI may need to be considered in WHO global hepatitis B elimination targets whilst acknowledging that the primary focus of eliminating HBsAg-positive chronic HBV infection is already challenging. There are multiple considerations to improve the OBI donor experience. Improving public health strategies and awareness campaigns to educate healthcare providers and societal communities would improve the knowledge of OBI, align the perceptions of risks among stakeholders, and reduce the stigma of HBV infection and its associated disease. Due to the lack of donor screening for OBI in low-to-middle-income countries, there is a need for affordable and validated point-of-care reflex HBV DNA tests[38] to identify donors with OBI and prevent HBV transmission by transfusion. Given the difficulty of OBI diagnosis and the unclear association with liver disease, health initiatives for research into OBI would be crucial to achieving the WHO's goal of eliminating viral hepatitis, especially in sub-Saharan Africa, where the burden of HBV is high. There is also a need to consider the resource constraints in low-resource and high-endemic settings when managing donors with OBI. For example, adequate diagnostic tools for follow-up and a strong linkage of blood services to community-based care are needed. As with the HIV epidemic, partnerships with non-governmental, international health organisations and wealthier nations would enable access to funding, expertise, and resources[39] that may be necessary for the management of individuals with OBI. Lastly, the cost-effectiveness of OBI management strategies compared to other public health interventions could be investigated, particularly in the context of low-to-middle-income countries.

Contributors

HH conceived the project. All authors were involved in expert consensus discussions. MXF, HH, WLI, and PS wrote the manuscript. All authors critically edited and, read and approved the final version of the manuscript.

Data sharing statement

No original data was used in this manuscript.

Declaration of interests

AE reports personal payments from GSK and Gilead and IUL reports personal payments from Roche Diagnostics and Roche Molecular Diagnostics. All other authors report no conflicts of interest that pertain to this work.

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