Infectivity of occult hepatitis B from two different points of view

Two manuscripts in this issue of **TRANSFUSION** assess the risk of transmission of occult hepatitis B (OBI) by transfusion and approaches to its prevention in Japan and in Europe. OBI is defined as the presence of circulating hepatitis B virus (HBV) DNA as detected by HBV nucleic acid test (NAT), in the absence of detectable HBV surface antigen (HBsAg), excluding the window period. During the window period of infection, HBV DNA is present but the immune system has not yet had the opportunity to generate antibodies to the several antigens of HBV, particularly HBV core (anti-HBc) and HBV surface (anti-HBs) antigens. In OBI anti-HBc is always detectable. In contrast, successful vaccination induces the formation of anti-HBs, which is protective, and HBV DNA is absent. It should be noted that the classification of an infection as OBI is entirely dependent on the sensitivity of the assays being used to detect HBV antigens, antibodies, and DNA.[1]

The name "occult HBV" can and is often misinterpreted because it conveys the impression that the etiologic agent is hidden somewhere in the body of the infected individual and is being missed by diagnostic tests, reminding us of "AIDS without HIV," a suggestion that caused major panic in the early 1990s and reignited concerns about the tragic epidemic of the early 1980s.[2] While HIV is the etiologic agent of AIDS, HBsAg is not the agent of hepatitis B. It is part of a family of small particles made of proteins and lipids that are produced and released by HBV-infected cells into the blood stream in high concentration at the same time that infectious viral particles are released. HBsAg can circulate with infectious HBV virus particles but can also circulate in the absence of HBV particles; HBsAg consequently is not itself infectious. However, it was the first recognized HBV antigen and became the most prominent and effective target of immunoassays for diagnosis of infection and for screening of blood donors. Until the more recent development of molecular assays, serologic assays for HBsAg have been the most important contributors to the safety of the blood supply with regard to hepatitis B.

Taira and colleagues[3] from the Japanese Red Cross (JRC) estimated the residual risk of transmission of HBV by donors with OBI. JRC had been screening blood donations for HBV using hemagglutination for HBsAg. Since 2008 all hemagglutination tests have been replaced by chemiluminescent enzyme immunoassay (CLEIA). JRC rejects donations that are positive for HBsAg and subjects negative donations to further determination of titers of anti-HBc and anti-HBs. It accepts donations with high titers of anti-HBs (≥200 IU/L) regardless of the titer of anti-HBc. However, it rejects donations with a high titer of anti-HBc and low titer of anti-HBs (Table 1 in Taira et al.[3]). In addition, all donations are tested for HBV DNA using minipool NAT (currently pools of 20 donations; previously pools of 50). Since four to 13 transfusion-transmitted infections continue to occur annually, the investigators performed retrospective individual-donation HBV NAT (ID-NAT) on a large number of samples from lookback and traceback cases that were stored in their extensive repository. Whenever possible they tested follow-up samples from recipients with suspected HBV transmission by transfusion. The donations tested by ID-NAT came from donors who had screened as negative for HBV DNA by HBV NAT performed in pools of 20 to 50 donations.

The authors also determined the impact of changes in their NAT screening algorithm since the introduction of molecular testing for HBV in 1999. When they compared the more sensitive TaqScreen currently performed in pools of 20 donations with the early AmpliNAT performed in pools of 50 donations they observed that the OBI detection rate increased from 3.9 to 15.2 per million and that the yield of window period donations decreased from 13.2 per million to 5.7 per million (Table 2 in Taira et al.[3]). The counterintuitive decline in yield of window phase NAT-yield donations after the reduction in pool size likely resulted from the introduction of the more sensitive CLEIA test for HBsAg in 2008, although a decline in HBV incidence may have also contributed to the overall reduction in DNA-only window phase infections.

The investigators concluded that approximately 2% of the donors with low titers of anti-HBc and anti-HBs presented low-level viremia and that this viremia did not correlate with anti-HBc titers, leading them to suggest that the best strategy to prevent transmission of HBV by donors with OBI requires elimination of all donations with low titers of anti-HBc and anti-HBs. In prior studies, JRC had estimated that the risk of transmission of HBV associated with donations with low titers of anti-HBc was 2.4% to 3.0%, 10 times lower than that of donors in the window period of HBV infection where the infectivity was estimated at 27%.[4] The authors calculate, based on the 3% rate of transfusion transmission attributed to OBI, that there would be 47 OBI transfusion transmissions that ID-NAT would prevent but some infectious units would also be missed due to fluctuating low-level

TRANSFUSION 2013;53:1379-1381.

viremia in OBI. Although ID-NAT would also reduce window period transmissions by 37%, the JRC elected to continue to perform HBV NAT in minipools of 20 donations and achieve maximum safety by discarding all units with low anti-HBc and anti-HBs titers, accounting for 1.3% of the total donations.

Allain and coworkers[5] estimated the risk of transmission of HBV by donors with OBI by aggregating information and specimens from donors with OBI identified in seven European countries and by performing additional testing on samples from these donors and their recipients. The donors were identified through lookback and traceback cases from seven blood centers in Croatia, Denmark, Germany, Poland, and Spain, and data generated in two virology laboratories in Germany and one in Cambridge, UK. Twenty-four OBI donors implicated in transfusion-transmitted HBV infections were identified, 19 through lookback and five through traceback of donors suspected of transmitting HBV to recipients subsequent to implementation of HBV NAT. The different centers used different donor screening assays available commercially and the virology laboratories performed additional studies that included determination of viral genotype, confirmation of transmissions by sequencing the pre-S/S region from 10 donor recipient pairs, and determination of viral loads of donations. Unfortunately, there were no direct data about the status of the infectious donation or pretransfusion information from recipients and in cases in which sequencing could not be performed transfusion transmission could not be definitively confirmed. Logistic regression analysis showed that the highest risk of transmission by transfusion, ranging from 25% to 100%, was associated with absence of anti-HBs in donors and recipients and the amount of plasma transfused. The authors recommended different risk mitigation strategies, depending on the prevalence of anti-HBc in the population: they suggested implementation of donor screening for anti-HBc when the prevalence among blood donors is less than 2% to 4%, and the implementation of sensitive HBV-NAT (optimally ID-NAT) when the prevalence is higher.

In essence, both groups of investigators showed an association of OBI in donors with transmission of HBV infection to recipients and also found that in some circumstances infectivity was dependent on product volume. In addition, both considered that anti-HBs could be protective (at some level). Finally, both hypothesized that ID-NAT and/or anti-HBc testing contributed to safety. The HBV transmission risks in the two studies were clearly different, likely a function of method and approach, subject selection, and existing donation screening policies.

The issue that we are still confronting with OBI is that we do not know its actual prevalence among blood donors and its contribution to the residual risk of transfusion-transmitted HBV in most regions of the world. The present articles contain suggestions that are applicable to the authors' settings, but cannot be comfortably generalized and do not allow construction of clear protocols for donor screening applicable everywhere because of the wide differences in burden of infection and disease in many countries. HBV NAT has had improvements in sensitivity leading some investigators to consider whether HBsAg screening with serologic methods is still a valuable test.[6] The major obstacle for the implementation of ID-NAT is the cost, particularly in the face of major expenditures in equipment and personnel in addition to the cost of assay kits required for a very limited safety benefit when compared to the cost of high sensitivity HBsAg assays performed in individual donations. Certainly the fact that the assays are in a triplex format, that is, include detection of HIV and HCV in addition to HBV, contributes to a reduction of these costs.

Some questions remain unanswered such as the prevalence and molecular and serologic characteristics of OBI infections in donors in various countries around the world besides North America, Europe, and Japan. Addition of screening for anti-HBs to the screening with anti-HBc could help countries with higher prevalence to improve safety without major disruption of the blood supply in the absence of HBV NAT implementation. Certainly, both articles provide additional supporting evidence for the protective effect of anti-HBs. However, it is clear that the implementation of HBV NAT has made a very important contribution to the safety of the blood supply, leading to residual risks comparable to those of HIV and HCV, so retention and even enhancements in sensitivity of HBV NAT screening should be considered. Finally, with the continued increase in the proportion of vaccinated populations around the world, there will be a future decrease in the burden of infection leading to a consequent decrease in the risk of HBV transmission by transfusion.[7]

CONFLICT OF INTEREST

None.

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