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Hepatitis B virus reactivation in hepatitis B core antibody positive lung transplant recipients

Oscar A. Fernandez-Garcia, MD,[a] Nathan Zelyas, MD, MSc,[b] Vanessa Meier-Stephenson, MD, PhD,[a] Kieran Halloran, MD, MSc,[c] and Karen Doucette, MD, MSc[a,*]

[a]*Division of Infectious Diseases, University of Alberta, Edmonton, Alberta, Canada;*
[b]*Department of Laboratory Medicine and Pathology, University of Alberta, Edmonton, Alberta, Canada;*
[c]*Division of Pulmonary Medicine, University of Alberta, Edmonton, Alberta, Canada.*

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BACKGROUND: Solid organ transplant recipients with resolved hepatitis B virus (HBV) infection are at risk for reactivation; however, most of the studies have focused on kidney transplant recipients and have short to intermediate term follow-up. Risk factors for reactivation are also uncertain, with some studies suggesting surface antibody (anti-HBs) may be protective.

METHODS: This retrospective single-center study aimed to assess the risk of HBV reactivation (HBVr) in lung transplant recipients with prior HBV infection as well as the value of anti-HBs titers in predicting HBVr. Surface antigen (HBsAg) negative, core antibody (anti-hepatitis B core (HBc)) positive adult lung and heart-lung solid organ transplant recipients from 2005 to 2019 were included. The primary outcome was HBVr after transplant, defined as seroreversion to HBsAg positivity. The secondary outcome compared anti-HBs titers at transplant and at post-transplant month 12.

RESULTS: The cohort included 38 lung and heart-lung recipients with anti-HBc positive, HBsAg negative pretransplant serology. Reactivation occurred in 3 of 38 (8%) at 49, 69, and 94 months post transplant. Two (5% of cohort) subjects died as a consequence of HBVr. Two of the 3 HBVr patients had anti-HBs titers > 10 IU/ml at transplant and 1 had anti-HBs > 100 IU/ml at time of HBV reactivation. We did not find a statistically significant decrease in anti-HBs titers 1 year after transplant in subjects with baseline anti-HBs > 10 IU/ml.

CONCLUSIONS: The prolonged time to reactivation highlights the lifelong risk. The 8% rate of reactivation and 5% mortality support a preferred strategy of indefinite HBV antiviral prophylaxis over monitoring in anti-HBc positive lung recipients.

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The worldwide burden of hepatitis B virus (HBV) infection is high. It is estimated that 3.6% of the global population is chronically infected (hepatitis B surface antigen [HBsAg] positive).[1] The prevalence of previous infection with HBV (hepatitis B core antibody [anti-HBc] positive) in the global population is estimated to be 21%.[2]

*Corresponding author: Karen Doucette, MD, MSc, University of Alberta, Division of Infectious Diseases, 8440 112 ST NW, Edmonton, Alberta T6G 2B7, Canada.
E-mail address: karen.doucette@ualberta.ca.

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Hepatitis B virus latently infects hepatocytes in the form of episomal covalently-closed circular DNA.[3] Despite virologic control and limitation of progressive liver disease, HBsAg loss does not represent sterilizing cure as covalently-closed circular DNA in hepatocytes remains replication competent. Potent immunosuppression may result in reactivation of viral replication, seroreversion to the HBsAg positive state, and progressive liver disease.[4] The presence of hepatitis B surface antibody (anti-HBs) titers ≥10 IU/ml has been traditionally equated with protective immunity and is associated with a lower probability of reactivation after chemotherapy.[4,5] In certain populations such as hematopoietic stem cell transplant recipients or people with advanced human immunodeficiency virus (HIV) infection, anti-HBs loss has been detected at the time of HBV reactivation (HBVr).[6,7]

In solid organ transplant recipients, hepatitis B reactivation has been mostly described in the kidney transplant population.[8] Jeon et al reported lower reactivation rates in anti-HBc positive patients with detectable anti-HBs (5.6% vs 1.2%).[9] There are few studies examining the risk of reactivation and outcomes in thoracic transplant recipients. The available literature focuses largely on HBsAg positive recipients or recipients of organs from HBsAg positive donors. [10-12]

Guidelines recommend that nonliver solid organ transplant recipients who are HBsAg negative, anti-HBc positive be monitored with HBsAg and HBV DNA every 3 to 6 months at least during the first post-transplant year. However, data are lacking to guide optimal prevention strategies and lung recipients are under-represented in the literature.[13]

The aim of this study was to assess the risk of HBVr in anti-HBc positive, HBsAg negative lung transplant recipients as well as the value of anti-HBs titers in monitoring for HBVr. In 2005, the study center implemented a clinical protocol to monitor anti-HBs titer in anti-HBc positive non-liver solid organ transplant recipients. Anti-HBs is measured at 1-, 3-, 6-, 9-, and 12-month post-transplant, under the hypothesis that antibody levels wane before hepatitis B reactivation occurs. Baseline HBV DNA is not routinely requested in this population. In those anti-HBc positive/anti-HBs negative at the time of transplant, as well as in those anti-HBc positive who drop their anti-HBs titers below 10 IU/ml during monitoring, HBV DNA and HBsAg are monitored every 3 months for the first post-transplant year. Thereafter, serologic monitoring with anti-HBs and HBsAg is performed yearly following the first post-transplant year.

Methods

Study design and outcomes

This was a retrospective cohort study of adult HBsAg negative, anti-HBc positive lung, and heart-lung recipients who received a transplant between 2005 and 2019 at the University of Alberta Hospital. Outcomes data were collected to December 2022. The study was performed in accordance with the Declaration of Helsinki and was approved by the University of Alberta Health Research Ethics Board (Pro00114193); need for informed consent was waived given the study design and inclusion of deceased subjects.

The primary outcome of the study was HBVr defined as post-transplant detection of HBsAg. The secondary outcome was comparing anti-HBs titers at transplant and post-transplant month 12 in subjects with anti-HBs > 10 IU/ml at baseline.

Serological assessment was performed with the AxSYM platform (HBsAg V2, CoreTM, CORE-M, AUSAB, HCV V3; Abbott Laboratories, Abbott Park, IL), it was switched over to ARCHITECT PLUS i2000SR (HBsAg Qualitative, Anti-HBc II, Anti-HBc IgM, Anti-HBs, Anti-HCV; Abbott Laboratories) in July 2011. Viral load was measured using the COBAS AmpliPrep/COBAS TaqMan HBV DNA assay (Roche Diagnostics, NJ).

Study criteria

We included adult (≥18 years of age) HBsAg negative lung or heart-lung recipients with pretransplant serology positive for anti-HBc, with or without anti-HBs, who received grafts from donors who were HBsAg and anti-HBc negative. Hepatitis B viral load is routinely measured in donors with risk factors for blood-borne infections. Recipients from donors with detectable HBV DNA were excluded from this study. We excluded subjects who died or were lost to follow-up before the first post-transplant month. Data collected included sex at birth, age, indication for transplant, hepatitis C virus (HCV) coinfection, HIV coinfection, cytomegalovirus donor/recipient serostatus, induction immunosuppression, follow-up time post-transplant, antirejection therapy, and development of post-transplant lymphoproliferative disorder. The HBV-specific data collected included anti-HBs, HBV DNA, and HBsAg at transplant and during follow-up. Subject follow-up time corresponded to the period between transplant and the last registered viral hepatitis serology determination.

Statistical analysis

Continuous variables were expressed as median and interquartile range. Categorical variables were expressed as percentages. The few cases of reactivation precluded statistical analysis; they are presented in a descriptive manner. Log-transformed anti-HBs level means at transplant and post-transplant month 12 were compared using a paired Student's *t*-test. Stata version 14.1 (StataCorp LLC, College Station, TX) was used for data analysis.

Results

During the study period 675 lung/heart-lung transplants were performed at the study center. Forty-nine subjects met inclusion criteria, 11 were excluded due to transfer to another province after transplant and lack of follow-up data at the study center.

The characteristics of the 38 subjects included for analysis are summarized in Table 1.

Median follow-up time was 14 months (interquartile range (IQR), 11-62). The majority were double lung transplants, in addition to 4 heart-lung recipients. Recipients receive either IL-2 receptor antagonist or antithymocyte globulin induction based on immunologic risk. Maintenance immunosuppression employs tacrolimus, mycophenolate mofetil, and corticosteroids. Human immunodeficiency virus was present at transplant in 1 subject (3%) and 15 (39%) had history of HCV infection. Two subjects (5%) received post-transplant HCV direct acting antiviral therapy. Two (5%) patients received post-transplant HBV

Table 1 Baseline Characteristics

Variable	*n* = 38
Age, years (IQR)	56 (50-60)
Male sex	28 (76)
Transplant type	
Double lung	33 (89%)
Heart-lung recipients	4 (11%)
Indication for transplant	
COPD	12 (31%)
Pulmonary talcosis	11 (29%)
IPF	4 (11%)
PAH	2 (5%)
CHD	2 (5%)
Other	7 (19%)
Induction immunosuppression	
IL2RA	28 (73%)
ATG	10 (27%)
HIV coinfection	1 (3%)
HCV coinfection	15 (39%)
Anti-HBs at transplant IU/ml (IQR)	28 (10.8-131.8)

Abbreviations: Anti-HBs, antihepatitis B surface antigen antibody; ATG, antithymocyte globulin; CHD, congenital heart disease; COPD, chronic obstructive pulmonary disease; DAA, direct acting antiviral; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IL2-RA, interleukin 2 receptor antagonist; IPF, idiopathic pulmonary fibrosis; IQR, interquartile range; PAH, pulmonary arterial hypertension; PTLD, post-transplant lymphoproliferative disorder.

prophylaxis, 1 with continuous tenofovir disoproxil fumarate as part of antiretroviral therapy for HIV coinfection; the other subject received lamivudine for the first post-transplant year. Only 1 (2%) subject developed post-transplant lymphoproliferative disorder and received rituximab during follow-up. None of the subjects received augmented immunosuppression, such as antithymocyte globulin or high dose steroids, as treatment of rejection for the duration of follow-up.

The primary outcome, detection of HBsAg, occurred in 3 (8%) subjects. Their characteristics are depicted in Table 2**.** The cases were detected at 49-, 69-, and 94-month post-transplant. All 3 had elevated liver enzymes and high viral loads at diagnosis of HBVr.

Two (5%) of the subjects had a fatal outcome attributable to reactivation. The first subject had HBsAg detected 49 months after transplant when he presented with ascites. The patient developed hepatocellular carcinoma and died from disease progression 28 months after seroreversion was documented despite antiviral therapy with entecavir and resolution of ascites. This subject had a history of remote HCV infection cured years prior to transplant. Liver elastography performed as part of an unrelated research study 1 year prior to seroreversion documented no evidence of significant hepatic fibrosis. The second subject had seroreversion detected 69 months after lung transplant when diagnosed with jaundice, ascites, coagulopathy, and rising ammonia. Liver biopsy was not performed given progression to multiple organ failure. Other causes of liver disease, including viral infections, metabolic, autoimmune or toxic exposures, were excluded and imaging was not suggestive of other etiology. The subject died due to progressive liver failure 1 month after seroreversion was documented despite initiation of antiviral therapy with entecavir at diagnosis. Death was attributed to hepatitis B reactivation. The third subject was detected 94 months after transplant during predialysis workup and started on antiviral therapy with entecavir. This patient has not had complications attributable to HBVr.

Overall adherence to serological monitoring was suboptimal. Subjects had a median of 3 (1-3) HBsAg determinations. Reactivation events were not detected by the monitoring protocol, but rather picked up at the time of testing for clinical reasons or screening in the setting of other medical diagnoses.

Two of the subjects with HBVr had anti-HBs > 10 IU/ml at transplant. Patient 2, who presented with acute liver failure, had anti-HBs titer of 88.8 IU/ml at transplant and 62.9 IU/ml at post-transplant month 12. His anti-HBs titer was 3.9 IU/ml when HBVr was documented. Patient 3 detected during dialysis workup had an anti-HBs titer of 276.9 IU/at transplant, 134.7 IU/ml at post-transplant month 12, and 134.54 IU/ml when HBVr was documented. Patient 1 who developed hepatocellular carcinoma had anti-HBs < 10 IU/ml at transplant.

In the remainder of the cohort, 12 subjects had anti-HBs at transplant > 10 IU/ml and had a follow-up determination at month 12. Anti-HBs titers were not significantly different between both time periods, 41.8 IU/ml (22.1-41.8) vs 46.69 IU/ml (20.2-46.6), means 1.72 log ± 0.51 vs 1.58 log ± 0.33, $p = 0.26$.

Discussion

We documented 3 cases of HBV reactivation (8%) in this cohort of lung transplant recipients, notably presenting beyond 1-year post-transplant with fatal outcomes in 2 of these 3. Hepatitis B related complications accounted for 5% of deaths in this cohort.

The role that "protective" anti-HBs titers may be playing in these subjects is worth exploring. Two recipients had levels of anti-HBs that would be considered protective at

Table 2 Characteristics of the Subjects With Hepatitis B Reactivation

Age, years	Sex	Induction	Anti-HBs at transplant UI/ml	Anti-HBs at reactivation UI/ml	Viral load at reactivation	Outcome
54	Male	Daclizumab	< 10	< 10	7.88 log	Death, HCC
48	Male	Daclizumab	88.8	3.93	7.8 log	Death, ALF
56	Female	Basiliximab	276.9	134.4	8.51 log	On therapy

Abbreviations: ALF, acute liver failure; HCC, hepatocellular carcinoma.

transplant and 1 had an anti-HBs titer > 100 IU/ml when reactivation was documented. Our observations of "protective" anti-HBs titers at the time of reactivation casts doubt on the hypothesis that anti-HBs levels fall to "non-protective" levels before reactivation in the setting of immunosuppression posttransplant. A Japanese cohort of patients with rheumatic disease receiving biologic agents reported a similar phenomenon where some patients with anti-HBs levels > 10 IU/ml had detectable fluctuating HBV DNA.[14] A more recent study on kidney transplant recipients also found instances of reactivation in patients with detectable anti-HBs.[15] This is consistent with the observation that patients with chronic hepatitis B who have coexistence of anti-HBs and HBsAg have been found to have antibodies whose specificity does not match the infecting viral subtype.[16] Furthermore, anti-HBs antibody titers, where measured, remained stable in the first year post-transplant in this population. This finding in addition to the case of reactivation with an anti-HBs titer > 100 IU/ml suggests that following anti-HBs titers is not a useful monitoring strategy in anti-HBc positive lung transplant recipients.

Recommendations for prevention of hepatitis B reactivation in immunosuppressed populations are guided by the incidence of HBVr under the specific immunosuppressive agent.[6,13,17-20] Populations with an incidence < 1% are considered at low risk and do not warrant prophylaxis. Universal prophylaxis is recommended where the incidence of HBVr is greater than 10%. Moderate risk of reactivation is defined by an incidence of 1% to 10%, in this category, recommendations for preventing HBVr are heterogeneous.[17] Both the American Gastroenterology Association (AGA) and a recent expert consensus recommend prophylaxis over monitoring in this population.[17,18] The European Association for Study of the Liver recommends serologic and molecular monitoring over prophylaxis (preemptive therapy).[19] All these recommendations are focused on patients undergoing antineoplastic, biologic, or corticosteroid therapy where prophylaxis is often restricted to the period of maximal, and/or time-limited, immunosuppression. In contrast, immunosuppression in lung recipients is profound and prolonged. Risk of reactivation is maintained lifelong as reflected by the late documentation of reactivation in our study.

Transplant-specific guidelines recommend monitoring every 3 to 6 months for at least the first post-transplant year.[13] The Kidney Disease Improving Global outcomes Guidelines specifically recommend against antiviral prophylaxis in kidney recipients and recommend monitoring with HBsAg and HBV DNA for a minimum of 1 year.[20] Based on our study, we believe it is more appropriate to follow the general principles established by the AGA guidelines for immunosuppression and HBVr and favor the administration of indefinite prophylaxis in lung recipients.[18]

The incidence of reactivation documented in our cohort places lung transplant recipients in the moderate risk category. It is worthwhile mentioning that reactivation in the literature is not only defined by HBsAg seroreversion. A recent consensus has defined reactivation as HBsAg seroreversion or an increase of at least 1 log IU/ml in the viral load of subjects with undetectable HBsAg but detectable anti-HBc.[21] Subjects in our cohort did not have HBV DNA measured at transplant so documentation of reactivation for the purpose of the study was limited to those with HBsAg seroreversion. It is reasonable to hypothesize that had HBV DNA been closely monitored we would have documented a higher incidence of reactivation, by consensus definition, crossing the 10% high risk threshold. Most worrisome were the severe outcomes associated with reactivation in our cohort. As observed in one of our cases, acute liver failure due to hepatitis B reactivation may not be reversible with antiviral therapy and high mortality is expected despite therapy.[22]

There are several limitations to this study. Patients transplanted at the study center and followed at other sites were excluded. However, assuming none of the 11 excluded subjects developed reactivation, the incidence in the cohort would still fall in the moderate risk range. The lack of routine HBV DNA monitoring opens the possibility of undetected HBsAg negative reactivation. Still, the prognostic relevance of HBsAg negative, HBV DNA positive reactivation is unknown. Finally, 11 patients did not have anti-HBs measured at transplant, limiting the inferences that can be made regarding anti-HBs titer analysis. Although missing data are acknowledged as a limitation, this does not invalidate the observations as described above; it highlights the challenges of real-world adherence to an indefinite monitoring protocol post-transplant.

Based on the risk of reactivation observed in this study, the lack of evidence-based surveillance protocols, the apparent lack of predictive value of anti-HBs titers, the potentially life-threatening nature of HBV reactivation, and the well-documented long-term safety of HBV antivirals, we conclude that a universal prophylaxis strategy is preferred in anti-HBc positive, HBsAg negative lung transplant recipients. An argument can be made that both universal prophylaxis or universal monitoring are oversimplified strategies and a more individualized approach might be preferred. Regrettably, the ability to individualize management is limited due to the lack of reliable predictors of adverse outcomes. Indefinite HBV antiviral prophylaxis in anti-HBc positive lung transplant recipients is aligned with the recommendations of the AGA guidelines and the more recent consensus.[17,18]

The use of universal prophylaxis may have some caveats; this strategy depends on available medication coverage and its feasibility will be center dependent. It is probably worthwhile in settings where the resource is available. In settings where medication coverage is not available for prophylaxis, strict adherence to indefinite monitoring with HBV DNA, HBsAg, and liver enzymes may be reasonable.[23]

Conclusions

Hepatitis B reactivation among anti-HBc positive lung recipients is not uncommon, occurring in 8% of subjects in our cohort. Importantly, reactivation may occur despite detectable anti-HBs and protective titers at transplant. This study sheds light on the heterogeneity of HBV reactivation and the often-assumed protective role of anti-HBs. Our study suggests that monitoring anti-HBs levels in anti-HBc positive recipients may not predict reactivation. Our study

also demonstrates that hepatitis B reactivation occurs late after transplant. Unless lifelong regular surveillance can be assured, the rate of reactivation and lack of time-bound risk for this potentially life-threatening complication warrants indefinite antiviral prophylaxis.

Disclosure statement

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Declaration of Generative AI and AI-assisted technologies in the writing process

Generative AI or AI associated technologies were not used in the writing process of this manuscript.

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