[17] **Scott CL**, **T'Jonck W**, Martens L, Todorov H, Sichien D, Soen B, et al. The transcription factor ZEB2 is required to maintain the tissue-specific identities of macrophages. Immunity 2018;49, 312-325.e315.
[18] **MacParland SA**, **Liu JC**, **Ma XZ**, Innes BT, Bartczak AM, Gage BK, et al. Single cell RNA sequencing of human liver reveals distinct intrahepatic macrophage populations. Nat Commun 2018;9:4383.
[19] **Huang W**, **Metlakunta A**, Dedousis N, Zhang P, Sipula I, Dube JJ, et al. Depletion of liver Kupffer cells prevents the development of diet-induced hepatic steatosis and insulin resistance. Diabetes 2010;59:347–357.
[20] Reid DT, Reyes JL, McDonald BA, Vo T, Reimer RA, Eksteen B. Kupffer cells undergo fundamental changes during the development of experimental NASH and are critical in initiating liver damage and inflammation. PLoS ONE 2016;11 e0159524.
[21] Baratin M, Simon L, Jorquera A, Ghigo C, Dembele D, Nowak J, et al. T cell zone resident macrophages silently dispose of apoptotic cells in the lymph node. Immunity 2017;47, 349-362.e345.
[22] Roberts AW, Lee BL, Deguine J, John S, Shlomchik MJ, Barton GM. Tissue-resident macrophages are locally programmed for silent clearance of apoptotic cells. Immunity 2017;47, 913-927.e916.
[23] Uderhardt S, Martins AJ, Tsang JS, Lammermann T, Germain RN. Resident macrophages cloak tissue microlesions to prevent neutrophil-driven inflammatory damage. Cell 2019;177, 541-555.e517.

Katharina Borst[1,†]
Theresa Graalmann[2,3,†]
Ulrich Kalinke[2,4,*]
[1]*Institute of Neuropathology, Medical Faculty, University of Freiburg, Germany*
[2]*Institute for Experimental Infection Research, TWINCORE, Centre for Experimental and Clinical Infection Research, A Joint Venture between the Hanover Medical School and the Helmholtz Centre for Infection Research, Brunswick, Germany*
[3]*Clinic for Immunology and Rheumatology, Hannover Medical School, Hannover, Germany*
[4]*Cluster of Excellence – Resolving Infection Susceptibility (RESIST), Hannover Medical School, Hannover, Germany*
*Corresponding author. Address: Institute for Experimental Infection Research, TWINCORE, Centre for Experimental and Clinical Infection Research, Hannover, Germany. Tel.: +49 511220027100.
E-mail address: kalinke.ulrich@mh-hannover.de

† Authors contributed equally.

Liver transplantation using hepatitis B core positive grafts: Which is the optimal antiviral prophylaxis?

To the Editor:

We read with great interest the article by Wong *et al.*[1] regarding the impact of hepatitis B core antibody (anti-HBc) positive liver grafts on survival and risk of hepatitis B (HBV) infection after liver transplantation (LT). The authors evaluated 964 LT recipients who received anti-HBc positive (n = 416, 43.2%) or anti-HBc negative (n = 548, 56.8%) liver grafts. Interestingly, donor anti-HBc status had no impact on long-term patient and graft survival, irrespective of graft peri-operative characteristics and recipient model for end-stage liver disease score at the time of LT. This finding is very encouraging in the era of liver graft shortages, particularly as it did not confirm the results of a previous study[2] in which the use of anti-HBc positive liver grafts was associated with worse post-LT outcomes.

The authors also evaluated the risk of *de novo* HBV infection after LT.[1] There were 108 HBV surface antigen (HBsAg)-negative (38 both anti-HBc/anti-HBs positive, 22 anti-HBc positive only, 24 anti-HBs positive only, 24 both anti-HBc/anti-HBs negative) recipients who received liver grafts from anti-HBc positive donors. Of them, 64 received lamivudine and 44 entecavir monoprophylaxis post-LT. *De novo* HBV infection, defined as post-LT detectable serum HBsAg and/or HBV DNA in HBsAg-negative recipients, was observed in 4.7% of patients under lamivudine (3/64) and none of the patients under entecavir (0/44), a numerical but not statistically significant difference ($p = 0.269$). Based on this finding, Wong *et al.*[1] suggested that antiviral agents with a high barrier to resistance (*i.e.* entecavir or tenofovir) should be used as first-line antiviral prophylaxis in HBsAg-negative recipients who receive anti-HBc positive liver grafts, in contrast to the current international guidelines which recommend lamivudine in this setting.[3] However, we believe that the authors' suggestion was based on findings which need further interpretation and should be considered with caution. First, all 3 patients diagnosed with *de novo* HBV infection had repeatedly undetectable HBV DNA and were only diagnosed based on HBsAg seropositivity. This HBV negative/HBsAg positive serological pattern is of unclear clinical significance in HBV-transplant recipients.[4] Second, HBsAg was reported to be only transiently positive in 2 of these patients who soon became HBsAg-negative and eventually developed anti-HBs. The third patient was found to be HBsAg positive at 1 month post-LT and presumably remained HBsAg positive (it is not clearly stated in the paper), but had undetectable serum HBV DNA on several occasions and no evidence of HBV-related histological lesions on 3 liver graft biopsies which were all negative for immunohistochemical staining for HBsAg and HBcAg. Third, the impact of the recipient's anti-HBc/anti-HBs combination status in relation to the type of HBV prophylaxis (lamivudine or entecavir) was not reported, although it has been shown to affect the probability of *de novo* HBV infection in this setting.[4] In particular, our previous systematic review[4] showed that the risk of *de novo* HBV infection in HBsAg-negative recipients who receive anti-HBc positive liver grafts but no antiviral prophylaxis after LT is just 1.4% in recipients positive for both anti-HBc and anti-HBs, but as high as 13.1% or 9.7% in those positive for only anti-HBc or anti-HBs. In agreement with the latter findings, the authors reported that none of the 38 recipients positive for both anti-HBc and anti-HBs developed

Keywords: Hepatitis B core antibody; Liver transplant; Hepatitis B; Hepatitis B core antibody positive graft; *De novo* hepatitis B infection.

de novo HBV infection under any type of antiviral prophylaxis (lamivudine or entecavir) in their study.[1]

In conclusion, the recommendation of this study[1] for universal use of high genetic barrier agents instead of lamivudine in HBsAg negative recipients of anti-HBc positive grafts is not based on strong data and certainly needs additional exploration in larger, ideally randomized, studies with careful evaluation of the risk of *de novo* HBV infection in all subgroups of such LT recipients. Until then, we believe that (in accordance with the current guidelines[3]), HBsAg-negative recipients of anti-HBc positive grafts can continue to receive prophylaxis with lamivudine, while both anti-HBc/anti-HBs positive recipients may need no anti-HBV prophylaxis at all.

Financial support

The authors received no financial support to produce this manuscript.

Conflict of interest

Evangelos Cholongitas: Evangelos Cholongitas has served as advisor/lecturer and/or has received research grants for Abbvie, Astellas, Bristol- Myers Squibb, Gilead, Merck Sharp & Dohme, Novartis and Regulus Therapeutics and Tiziana Pharmaceuticals. George V. Papatheodoridis has served as advisor/lecturer for Abbvie, Bristol- Myers Squibb, Gilead, GlaxoSmithKline, Janssen, Merck Sharp & Dohme, Novartis and Roche; has received research grants from Abbvie, Bristol- Myers Squibb, Gilead, Janssen and Roche; has participated in clinical trials of Abbvie, Bristol- Myers Squibb, Gilead, Janssen, Merck Sharp & Dohme, Novo Nordisc, Regulus Therapeutics and Tiziana Pharmaceuticals; was in the Data Safety Management Board for Gilead.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

Evangelos Cholongitas and George V. Papatheodoridis contributed equally in this paper

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2019.05.004.

References

[1] Wong TC, Fung JY, Cui TY, Lam AH, Dai JW, Chan AC, et al. Liver transplantation using hepatitis B core positive grafts with antiviral monotherapy prophylaxis. J Hepatol 2019;70:1114–1122.
[2] Angelico M, Nardi A, Marianelli T, Caccamo L, Romagnoli R, Tisone G, et al. Hepatitis B-core antibody positive donors in liver transplantation and their impact on graft survival: evidence from the Liver Match cohort study. J Hepatol 2013;58:715–723.
[3] European Association for the Study of the Liver, Electronic address: easloffice@easloffice.eu, European Association for the Study of the Liver. EASL Clinical Practice Guidelines on the management of hepatitis B virus infection. J Hepatol 2017;2017:370–398.
[4] Cholongitas E, Papatheodoridis GV, Burroughs AK. Liver grafts from anti-hepatitis B core positive donors: a systematic review. J Hepatol 2010;52:272–279.

Evangelos Cholongitas[1]
George V. Papatheodoridis[2,*]
[1]*First Department of Internal Medicine, Medical School of National & Kapodistrian University of Athens, Laiko General Hospital, Greece*
[2]*Academic Department of Gastroenterology, Medical School of National and Kapodistrian University of Athens, Athens, Greece*
*Corresponding author. Address: Department of Gastroenterology, Medical School of National and Kapodistrian, University of Athens, Laiko General Hospital of Athens, 17 Agiou Thoma Street, 11527 Athens, Greece. Tel.: +30 2132061115; fax: +30 2107462601.
E-mail address: gepapath@med.uoa.gr

Reply to "Liver transplantation using hepatitis B core positive grafts: Which is the optimal antiviral prophylaxis?"

To the Editor:

We appreciate the interest and comments by Cholongitas and Papatheodoridis. *De novo* hepatitis B viral (HBV) infection was defined as HBV surface antigen (HBsAg) seropositivity and/or detectable HBV DNA in a non-HBV recipient. This is a widely adopted definition, and as all HBV naïve recipients were covered with antiviral therapy after receiving hepatitis B core antibody (anti-HBc) positive grafts in our study,[1] it would be highly unlikely for them to develop detectable HBV DNA. As the patients were on antiviral therapy, viral activity would be suppressed, and may explain the transient nature of HBsAg positivity in these patients. Moreover, in the histological study of patients with chronic HBV who remain HBsAg positive after transplantation on entecavir therapy, all stained negative for HBsAg.[2] We agree that the anti-HBc+/anti-HBs+ represents the lowest risk group. However, with the high number of anti-HBc+ grafts being used in our region, even a small percentage of *de novo* infection would be a significant risk. Previous studies have shown that using less potent agents with high resistance rates is associated with *de novo* infection and the development of resistance with longer follow-up.[3–5] Therefore, we would recommend adopting agents with better resistance profiles now that they are widely available.

Financial support

The authors received no financial support to produce this manuscript.

Conflict of interest

The authors declare no conflicts of interest that pertain to this work.