Persistent hepatitis B virus (HBV) infection has been and still is a leading cause for end-stage liver disease in endemic regions in Asia and Africa. In contrast, in the Western hemisphere, the rates of HBV infection in liver transplant candidates is lower and declining as reflected in a recent UNOS analysis, reporting a 5.3% rate of HBV infection as the cause for liver failure and HBV associated hepatocellular carcinoma among 48,654 liver transplant candidates in the US [1]. The ongoing worldwide organ shortage for liver transplantation (LTx) has been a driving force for exploring new means to expand the pool of potential organ donors. Depending on the age of acquisition, acute HBV infection resolves spontaneously in up to ~90% of infected adults with an intact immune system. Consequently, the pool of potential liver donors includes a fraction of either anti-HBs+/anti-HBc+ or HBsAg−/anti-HBs−/anti-HBc+ individuals with normal liver functions who have such recovered from HBV infection. The size of this pool is driven by the particular prevalence of HBV infection in designated regions worldwide ranging between 1.8% and 6% in the US (between 1994 and 2006) as compared for example to 63% (2003) in Taiwan [2,3]. A retrospective survey among 35,620 cadaveric adult transplant recipients in the US (1994–2006) identified up to 8.5% anti-HBc+ donors. Understandably, the safety of using livers from such potential donors has initially been challenged due to the presence of occult HBV infection in some of the grafts, manifested by residual hepatic intra-nuclear cccHBV-DNA even in anti-HBc+/anti-HBs+ individuals, which can serve as a template for post transplantation HBV reactivation in immune suppressed recipients. More than two decades have passed since the first reports on transmission of occult HBV infection from HBsAg−/anti-HBc+ or anti-HBs−/anti-HBc+ liver transplant donors to HBV naïve recipients [4–7]. It soon became clear that the risk of HBV reactivation or de novo infection in recipients of such previously infected grafts may reach 75–80% in HBV naïve recipients, declining to 15–20% in anti-HBc+ or anti-HBs+ patients and to 0–5% in anti-HBs+/anti-HBc+ individuals. Meanwhile the development of potent nucleotide analogues as well as hepatitis B immune globulin (HBIG) provide excellent means to protect HBV naïve or even anti-HBc+ liver graft recipients against either de novo or reactivation of HBV infection. Consequently there is by now almost worldwide consensus that anti-HBc+ as well as anti-HBc+/anti-HBs+ grafts can be transplanted to matched patients with overt, occult or past HBV infection (and under certain circumstances in emergency conditions and with some precautions even to HBV naïve recipients). Recipients of such organs were reported to have an overall similar post transplant survival (with some exceptions [8]) as compared to anti-HBc−/HBsAg− naïve donors [2,9–14]. The current approach to the utilization of such grafts is reflected in the results of a 2007 international survey suggesting that most transplant centres will accept anti-HBc+ grafts even for HBV naïve recipients [15]. It took almost a decade to evaluate the advantages, the short term and intermediate safety and the limitations of using liver transplant grafts with occult HBV infection for patients with liver failure. Although data on long-term follow-up and safety in recipients of anti-HBc+ grafts are still unavailable, there is already a consensus as quoted from a recent editorial in the Journal of Hepatology by Cholangitas et al.: “Liver grafts from anti-HBc positive donors can be safely used, preferentially in HBsAg-positive or anti-HBc/anti-HBs positive recipients. HBsAg-negative recipients should receive prophylaxis with lamivudine, while both anti-HBc and anti-HBs positive recipients may need no prophylaxis at all” [14]. A similar view is expressed in the title of an editorial by M. Prieto “Antibody to hepatitis B core antigen-positive grafts: Not perfect but no longer marginal” [12].

Attention is now shifting to explore further means for expansion of the donor pool through utilization of HBsAg+ grafts from donors with overt HBV infection but with preserved liver function and without significant fibrosis for HBsAg+ recipients. The first case report on the utilization of HBsAg+ grafts appeared in 1994 [16] followed by more case reports between 2005 and 2007 [16–20]. Single centre reports on small series of patients receiving HBsAg+ grafts in 6–10 patients [21–23] followed by a larger study in 92 liver transplant recipients [24], paved the road for exploring this avenue of salvage further. A recent retrospective analysis of the US national data base (N = 78) confirmed that transplantation of HBsAg+ grafts, mainly in recipients with a history of HBV infection, did not reduce graft and patients survival post transplantation, provided recipients...
were protected with anti-viral therapy [25]. In the study using US national registry data, the 5-year HBsAg+ patient survival was 71% compared to 71% in the control group with a graft survival of 66% and 64% for recipients of HBsAg+ grafts and matched controls, respectively. Yet, the worldwide experience using HBsAg+ liver grafts is limited. In the present issue of the Journal of Hepatology, Yu and co-workers report their experience in a cohort of 42 adult Chinese patients who underwent liver transplantation with an HBsAg+ graft [26].

In this study, the investigators have retrospectively compared the short-term follow-up as well as the clinical, laboratory and serologic postoperative course and outcome of 42 orthotopic liver transplant recipients from HBsAg+ donors to 327 LTx recipients from HBsAg– donors. Among the HBsAg+ positive graft recipients, 38 patients survived more than 1 month and the maximal follow-up period was about 3 years. The overall mean follow-up for the recipients of an HBV positive graft was 13.9 ± 11.2 months as compared to 19 ± 11.8 months for the control group (p < 0.01). Among the 327 patients in the control group, 25.7% had apparently some HBV marker (details not mentioned) as a result of past exposure to HBV while 4/42 LTx patients who received an HBsAg+ graft were apparently HBV naïve.

The main results of the study include: (1) The immediate rates of postoperative morbidity and mortality as reflected by follow-up of primary graft non-function, acute rejection, biliary complications and liver function tests were similar in both study groups. (2) Since HBsAg positivity persists in recipients of HBV infected grafts, anti-viral treatment with a nucleos(t)ide analogue should be continued for an indefinite period postoperatively but there is no rational in the administration of HBIG in such patients. (3) Immune suppressive treatment of HBsAg+ patients receiving an HBsAg+ graft did not result in overt HBV reactivation. (4) All in all, transplantation of HBsAg+ grafts from HBV infected patients with preserved liver functions and presumably no significant liver disease to HBsAg+ recipients is a legitimate means to provide rescue for LTx candidates when no HBV naïve or anti-HBc+/HBsAg– donors are available.

**Comments**

The results of this study confirm previous retrospective observations regarding the utility of using HBsAg+ grafts in situations where no other options such as an HBV naïve cadaveric or living related donor are available. Thus, these results provide further justification for expanding the donor pool, especially in countries endemic for HBV such as China where the current prevalence of HBsAg is around 7% [27], not to speak of a rather high anti-HBc+ rate. Furthermore, as also reported previously, transplantation of HBsAg+ grafts may likewise be considered under special circumstances when other options are unavailable even for HBV negative recipients (with adequate anti-viral protection) as well as for anti-HBc+ and or anti-HBs+ patients with liver failure. The paper by Yu and coworkers is well written although the study design and results have some limitations as acknowledged by the authors. These include among others the retrospective and partially controlled design of the study; the relatively short-term follow-up, which does not enable a firm conclusion regarding the long-term safety and assessment of HBV associated complications. Interestingly, most organ recipients from HBsAg+ donors maintained an HBeAg+ status post transplantation, regardless of their original HBeAg or anti-HBe status prior to transplantation. This observation justifies a more in depth analysis including quantitative serum, intrahepatocellular and cccHBV-DNA measurements, genotyping and comparative sequencing of HBV-DNA with phylogenetic analysis in donors and recipients alike. In this context it is worthwhile to cite a previous report from Hong-Kong [28] and an accompanying editorial [29] describing a so called competition between two occult hepatitis B virus infections, which originated from an anti-HBc+ donor whose liver was transplanted to a patient with occult HBV who has previously been infected with HBV as well and treated with lamivudine. Therefore, further studies should include long-term monitoring of these parameters, which should lead to better understanding of the molecular pathophysiology in such patients, including the impact of genotype on the natural history of the graft. Finally, there are other, albeit experimental means for providing protection against HBV to graft recipients which remain to be explored, including adoptive transfer of immunity from anti-HBs positive donors to recipients [30] or immunization with a PreS/S vaccine [31,32].

In conclusion, the results of this chinese study by Yu and co-workers confirm and complement a number of previous observations from Europe and the US regarding the utility and short-term safety of LTx using HBsAg+ donors for HBsAg+ recipients. At present, data from a prospectively adequately controlled trial are unavailable. The logistics of conducting such a study in the future are complex and it is doubtful that results will be available in the near future. Meanwhile, and until then, it is the opinion of this viewer that the already obtained evidence justifies the use of HBsAg+ donors for patient persistently infected with HBV and liver failure when no other donor is available. However, in the absence of data regarding the safety of using grafts from HBsAg+ donors with delta virus co-infection, or vice versa transplanting HBsAg(+) grafts to delta virus infected recipients, caution is advised regarding approval of transplantation in such a situation. Not less important, further long-term follow-up is required for those HBsAg+ LTx recipients who have already received a graft from an HBsAg+ donor.

**Conflict of interest**

The author declared that he does not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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