

CORE TIP: Aim of this review is to summarize the current concepts and management of hepatitis B after liver transplantation. There are no clear guidelines regarding hepatitis B therapy after transplantation. HBIG is expensive and cumbersome to administer and there is no definite time point for discontinuation of hepatitis B immunoglobulin after liver transplantation. Here we summarize the indications and duration of hepatitis B immunoglobulin and nucleoside analogs. This review also addresses key molecular mechanisms and the risk factors which are associated with HBV reactivation post liver transplantation. This review provides up-to-date information not only for the liver transplant specialists but also for the virologists and scientists working in this field.

Point-to-point answers to Reviewer 1 (Code: 00722050)

Comment 1: The manuscript dealing with Reactivation of Hepatitis B After Liver Transplantation is an important contribution. The manuscript can be improved targeting three aspects. The first aspect is the pediatric one that needs to be expanded.

Response 1: We appreciated the feedback, and thank the reviewer for their suggestions to further improve the manuscript. .. HBV reactivation in pediatric liver transplant settings is a highly specialized area and require a dedicated review addressing all the key issues related to the HBV reactivation in pediatric liver transplant patients. We also think that inclusion of pediatric liver transplant group will dilute the overall purpose of the present review i.e HBV reactivation in the adult liver transplant population and thus we would like to limit this review to adult population.

Comment 2: The second is the occurrence of genomic mutations such as single nucleotide insertion in the 5'-untranslated region of hepatitis C virus with clearance of the viral RNA in a liver transplant recipient during acute HBV superinfection (please read and cite this article in Liver 2002: Liver. 2002 Feb;22(1):79-82. PMID: 11906622). The superinfection needs to be highlighted in the manuscript and it will make a comprehensive manuscript.

Response 2: Thank you for this valuable suggestion. In the revised manuscript, a complete section on "role of superinfection in HBV reactivation" is included in page number 7.

Comment 3: The third is the lack of histologic figures. I think it would be very beneficial if the authors liaise with a local pathologist to show the reactivation using some slides of re-activation by immunohistochemistry or in situ hybridization.

Response 3: Thank you, this is indeed a relevant suggestion. In page number 39, we have added two figures i.e. Fig 1a and Fig 1b. Fig1 a is about recurrent HBV infection leading to cirrhosis in a post-LT patient and Fig 1b is on immunostaining of HBV core antigen.

Point-to-point answers to Reviewer 2 (Code: 02528832)

Comment 1: Perhaps the authors could add some comments about the role of co-existing delta virus infection, and also about the influence of some genetic variations of the host genotype, since there are some studies that suggest a modulation of the outcome of LT-HBV patients. Globally, I find the review updated, interesting and well-structured.

Response 1: Thank you very much for your comment and suggestions. In page number 5, a new section on “Co-existing hepatitis D virus infection and HBV reactivation” has been added. In addition, as suggested, we have also included a new section on genetic variants on cytotoxic T lymphocyte antigen-4 (CTLA-4) single nucleotide polymorphisms on page number 6.

Point-to-point answers to Reviewer 3 (Code: 00504591)

Comment 1: The integration in the host liver genome is specific to the liver transplantation setting? If no, this section should be deleted or shorted.

Response 1: As suggested we have shortened this section and is given on page number 8.

Comment 2: The section Prophylaxis for HBV reactivation after liver transplantation In some subsections, A or B is attached and in the others, no symbols are attached. Please unify or explain the relationship among the subsections on the section Prophylaxis for HBV reactivation after liver transplantation.

Response 2: This has been changed.

Comment 3: Please explain the reason why no prophylaxis is needed when anti HBc and anti HBs are positive.

Response 3: We agree this is a key point that need more clarification, and appreciate the comment. Several studies have shown no prophylaxis is needed when anti-HBc and anti-HBs are positive. The presence of anti-HBs seems to protect from *de novo* HBV infection and both anti-HBc and anti-HBs-positive recipients represent a low risk group that can safely receive anti-HBc-positive liver grafts without any post-transplant HBV prophylaxis (probability of *de novo* HBV infection <2%). This has been added to the manuscript with references of the studies to support this finding. We however, have taken a moderate approach by recommending periodic HBV DNA level along with ALT to monitor for any relapse.

Point-to-point answers to Reviewer 4 (Code: 01551089)

Comment 1: this review lacks abstract and key words, which are important parts of a research.

Response 1: In the revised manuscript, abstract and the key words have been inserted.

Comment 2: The title of figures should not be written on the picture.

Response 2: Thanks, this has been changed.

Comment 3: Finally, as a review, it would be more helpful to have a figure which can conclude all parts you want to describe.

Response 3: Thank you for this valuable suggestion, in the revised manuscript, figure 2 on page 40 describes all the parts of the present review.