World Journal of Hepatology

REVIEW

Reactivation of hepatitis B after liver transplantation: Current knowledge, molecular mechanisms and implications in management

Ranjit Chauhan, Shilpa Lingala, Chiranjeevi Gadiparthi, Nivedita Lahiri, Smruti R Mohanty, Jian Wu, Tomasz I Michalak, Sanjaya K Satapathy

Ranjit Chauhan, Tomasz I Michalak, Molecular Virology and Hepatology Research Group, Division of BioMedical Sciences, Health Sciences Centre, Memorial University, St. John's, NL A1B 3V6, Canada

Shilpa Lingala, Chiranjeevi Gadiparthi, Sanjaya K Satapathy, Division of Transplant Surgery, Methodist University Hospital Transplant Institute, University of Tennessee Health Sciences Center, Memphis, TN 38104, United States

Nivedita Lahiri, Division of Rheumatology, Immunology and Allergy, Brigham Women's Hospital, Harvard Medical School, Boston, MA 02115, United States

Smruti R Mohanty, Division of Gastroenterology and Hepatobiliary Disease, New York-Presbyterian Brooklyn Methodist Hospital, Brooklyn, NY 11215, United States

Jian Wu, Department of Medical Microbiology, Key Laboratory of Molecular Virology, Fudan University School of Basic Medical Sciences, Shanghai 200032, China

ORCID number: Ranjit Chauhan (0000-0003-1682-0460); Shilpa Lingala (0000-0001-8219-2971); Chiranjeevi Gadiparthi (0000-0002-8905-6742); Nivedita Lahiri (0000-0002-7103-0202); Smruti R Mohanty (0000-0003-4887-5837); Jian Wu (0000-0001-9933-7364); Tomasz I Michalak (0000-0003-1438-0588); Sanjaya K Satapathy (0000-0003-0153-2829).

Abstract

Chronic hepatitis B (CHB) is a major global health problem affecting an estimated 350 million people with more than 786000 individuals dying annually due to complications, such as cirrhosis, liver failure and hepatocellular carcinoma (HCC). Liver transplantation (LT) is considered gold standard for treatment of hepatitis B virus (HBV)-related liver failure and HCC. However, post-transplant viral reactivation can be detrimental to allograft function, leading to poor survival. Prophylaxis with high-dose hepatitis B immunoglobulin (HBIG) and anti-viral drugs have achieved remarkable progress in LT by suppressing

viral replication and improving long-term survival. The combination of lamivudine (LAM) plus HBIG has been for many years the most widely used. However, life-long HBIG use is both cumbersome and costly, whereas long-term use of LAM results in resistant virus. Recently, in an effort to develop HBIG-free protocols, high potency nucleos(t)ide analogues, such as Entecavir or Tenofovir, have been tried either as monotherapy or in combination with low-dose HBIG with excellent results. Current focus is on novel antiviral targets, especially for covalently closed circular DNA (cccDNA), in an effort to eradicate HBV infection instead of viral suppression. However, there are several other molecular mechanisms through which HBV may reactivate and need equal attention. The purpose of this review is to address post-LT HBV reactivation, its risk factors, underlying molecular mechanisms, and recent advancements and future of anti-viral therapy.

Core tip: Aim of this review is to summarize the current concepts and management of hepatitis B after liver transplantation (LT). There are no clear guidelines regarding hepatitis B therapy after transplantation. Hepatitis B immunoglobulin (HBIG) is expensive and cumbersome to administer and there is no definite time point for discontinuation of HBIG after LT. 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 hepatitis B virus reactivation post LT. 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.

INTRODUCTION

Chronic hepatitis B (CHB) caused by hepatitis B virus (HBV) infection remains a major global health problem affecting an estimated 350 million people worldwide with more than 786000 individuals dying annually due to complications of CHB, including cirrhosis and liver cancer. CHB is the leading cause of hepatocellular carcinoma (HCC) accounting for at least 50% of newly diagnosed cases[1]. Furthermore, HCC is the third leading cause of cancer-related mortality in the world[2] with a dismal 5 year survival and the fastest growing rate of cancer death in North America[3]. Liver transplantation (LT) is the most effective treatment in patients with CHB-related liver failure, cirrhosis and HCC. However, HBV reactivation following LT emerges as a major clinical challenge[4].

Over the past decade, a substantial advancement has been made in the treatment of CHB, and to date several potent antiviral medications are available for the treatment of HBV infection, mainly gaining long-term viral suppression[5,6]. However, despite of having strong suppressive antiviral therapy for chronically HBV-infected patients, some patients still develop HCC possibly due to the presence of minimal residual viremia (MRV) and irreversible HBV DNA integration into liver genome. MRV is a consequence of persistent, low-level virus replication in the liver and at the extrahepatic sites, particularly in peripheral blood mononuclear cells (PBMC), coinciding with circulation of virus traces[7-10]. Despite long-term antiviral treatment with suppression of viral DNA, MRV commonly persist[7,11]. One of the major sources of MRV is supercoiled HBV covalently closed circular DNA (cccDNA) and its persistence is mainly responsible for recurrent HBV infection post-LT[12,13]. Prior to introduction of hepatitis B immunoglobulin (HBIG) in 1990s, HBV recurrence in LT was as high as 75% to 89% of patients with 3-year survival rate in 54%[14,15]. The introduction of viral suppression strategy using combination of HBIG and more potent nucleos(t)ide analogs (NAs) has significantly decreased the HBV recurrence in vast majority of these patients improving their long-term survival[16]. However, this strategy does not completely eradicate HBV and, therefore, does not protect against future recurrence of symptomatic HBV infection. It also requires monitoring of LT patients for life, thus significantly increasing the economic burden and manpower engagement.

Evaluating the risk of HBV recurrence is crucial in devising effective strategy against post-LT reactivation. The factors associated with high rates of HBV reactivation are high viral load prior to the transplant, HBV e antigen (HBeAg) reactivity, co-infection with human immunodeficiency virus type 1 (HIV), non-compliance with drug therapy, HCC at the time of LT, and anti-viral drug resistance. On the other hand, low viral load, anti-HBe positivity and anti-HBs presence are factors with lower risk of HBV reactivation[15,17-21].

MOLECULAR MECHANISMS OF HEPATITIS B REACTIVATION IN LIVER TREANSPLANTATION

cccDNA and its role in HBV reactivation

Although HBV is a DNA virus, it replicates by reverse transcription intermediate[22]. Establishment of cccDNA is crucial in the HBV life cycle. This nuclear cccDNA

minichromosomal acts as the powerhouse of HBV transcriptional machinery and constitutes a molecular basis for virus reactivation[12]. HBV cccDNA chronically exists throughout the natural history of HBV infection[23] and it is not yet possible to eradicate this HBV molecule even with current potent anti-viral therapies, such as Entecavir (ETV) or Tenofovir disoproxil fumarate (TDF)[24]. A recent study by Papatheodoritis *et al*[25] showed that despite of the anti-HBV therapy, HCC develops in the context of the cccDNA presence and, thus, MRV and reactivation cannot be ruled out.

When recipients receive transplantation with liver from donors with previous history of HBV infection, but with negative serum HBsAg and HBV DNA, intrahepatic cccDNA could still be detected after LT[4,26]. Notably, detection of anti-HBc alone in the absence of HBsAg and HBV DNA in a donor should be treated as an indicator of occult infection and a low-level virus replication in the liver, which could be reactivated post-LT[18,27,28]. On the other hand, patients with undetectable HBV viremia at LT and no evidence of cccDNA and intrahepatic HBV DNA on repeat examinations -may be safely withdrawn from long-term prophylaxis[29]. However, safe withdrawal also depends on the level of the sensitivity of the assays used for detecting HBV viremia, HBV cccDNA in the liver and the existence of HBV replication at the extrahepatic sites [*e.g.,* peripheral blood mononuclear cells (PBMC)], which in occult cases may be missed even using ultrasensitive tests.

Genotype-specific recurrence of HBV

Ten different HBV genotypes have been identified which are scattered in an ethno-geographically specific manner. Ample of evidence suggested the role of HBV genotypes in disease progression, mode of transmission, disease severity, HCC risk, and response to therapy[30]. Compared to genotype D, HBV genotype A responds well to the interferon therapy[31]. Numerous reports across the globe documented association of HBV genotype B and C with severe liver disease including development of HCC[32], while HBV genotype C has higher risk for mother to child transmission[33]. Since virus evolves within the host, study of HBV genotype is important prior to LT, especially in genotypes, which are associated with the occult HBV infection[34,35]. A study by Devarbhavi *et al*[34] demonstrated that patients with HBV genotype D have the highest risk of HBV recurrence and mortality compared to genotype A. In our recent study, we demonstrated that viral genotypes fluctuate while patient is on the Tenofovir therapy, revealing two important phenomena, first, there is mixture of viral populations present in HBV infected patient and secondly, at a given time, only one of the viral strain is inhibited/exhibits[36]. Although, not with regard to the HBV genotypes, but from the point of HBV quasispecies an elegant study by Buti *et al*[37] identified HBV quasi-species evolution after LT in patients under long-term lamivudine prophylaxis with or without HBIG

and there was low transient viremia detected even in the absence of serum HBsAg, showing importance of continuing HBV prophylaxis. In the same context, a recent case study by Mina *et al*[38] showed that HBV genotypes fluctuates after LT, which could possibly be the main reason behind the HBV reactivation in liver transplant settings. Since, in diagnostic assays, the possible source of HBV reactivation is negated, it is an open question, if extrahepatic tissues should be tested to find the origin of such reactivation. Studies focusing on HBV recurrence based on genotype are summarized in Table 1. It would be worthwhile to consider HBV genotyping in both donor and recipient so that each viral strain is tracked in case of the mixed genotype infections, which are emerging as important hidden source for reactivation.

Co-existing hepatitis D virus infection and HBV reactivation

Hepatitis delta virus (HDV) consists of a single-stranded RNA molecule enveloped by hepatitis B surface antigen (HBsAg)[39]. One of the risk factors of HBV recurrence in LT patients is the co-infection with hepatitis delta virus (HDV)[40]. Fulminant hepatitis B reactivation in co-infected patients has been reported[40,41]. HBsAg-positive liver grafts in HBsAg-positive recipients with HDV co-infection has been reported to result in virological recurrence and rapid development of liver cirrhosis, and need for re-transplant[42,43]. HDV is a RNA pathogenic virus that requires presence of HBV for its survival[44]. Studies on post-LT patients suggest that the absence of HBV prophylaxis or lack of proper function of HBIG leads to higher incidence of both HBV and HDV reinfection[43,45,46].

The co-existence or co-infection of HBV and HDV is very commonly observed, obviously due to the dependence of HDV infection on HBV. For instance, 11.9% of HBV-positive patients were also positive for HDV in an Italian liver patient cohort, with a higher incident in patients older than 50 years[47]. It also appears to have a geographical connection, as co-infection HBV-HDV in LT patients was found to be low in Japan[48], possibly due to the differential geographical distribution of HDV genotypes Ⅰ and Ⅱ between other parts of the world and Asian countries, respectively[49]. The helper functions of HBV provide the support to HDV for cell entry, replication, virion assembly and export[50]. The interactions between HBV-HDV occur in two phases, the first phase of active HDV replication occurs with the suppression of HBV, followed by reactivation of HBV and reduction in HDV in the second phase[51]. Due to this nature of HDV and HBV interactions, early recurrence of HDV has been detected in many patients in the absence of HBV recurrence[52]. Studies also imply that HDV could be a cause for many subclinical infections and symptoms develop rapidly upon recurrence of HBV[45]. HBV recurrence has been shown to cause atypical reappearance of HBV infection and HDV relapse in the

Table 1 Recurrence of hepatitis B virus in different genotypes

HBV genotype	No. of patients	Median follow-up (mo)	HBV recurrence number (%)	Mortality number (%)
Girlanda *et al*[175], 2004				
A	15	56	4 (27)	2 (13)
D	13	67	7 (54)	5 (38)
A/D	12	43	4 (33)	2 (17)
A/C	2	66	1 (50)	0
E	2	45	1 (50)	1 (50)
C	1	106	1 (100)	0
Devarbhavi *et al*[34], 2002				
A	10	56	3 (30)	1 (10)
C	6	22.5	3 (50)	1 (10)
D	5	15	3 (60)	1 (10)
E	1	1	0	Lost follow-up
Gaglio *et al*[176], 2008				
A	28	24	3 (10.7)	3 (10.7)
B	8	24	1 (12.5)	1 (12.5)
C	18	24	1 (5.5)	5 (5.5)
D	6	24	0	0
Lo *et al*[177], 2005				
B	43	36	4 (2)	7 (17)
C	74	36	21 (15)	7.5 (11)

HBV: Hepatitis B virus.

allographs[53]. Additionally, the recurrence of HBV-HDV post-LT is the cause of death for many LT patients, prompting need for more research on this subject[45,54]. In a recent study, recurrence rate of HBV after LT was not different from the recurrence rate of HBV-HDV co-infection on long-term low-dose HBIG prophylaxis along with TDF[55].

Genetic variations of host genetic makeup in predicting HBV reactivation

Genetic variations of host genetic makeup may play some role in increased/reduced risk of HBV reactivation after LT. Single-nucleotide polymorphisms (SNP) of two-gene locus cytotoxic T lymphocyte antigen-4 (CTLA-4) +49 and CD86 +1057 were previously reported to influence the outcome of LT with respect to allograft acceptance[56,57]. Homozygosity for CTLA-4 +49 (G/G genotype) was reported to be associated with reduced risk of HBV recurrence in post-LT Chinese patients[56]. CD86 and CTLA-4 are known to stimulate and inhibit T cell activation, respectively.

Role of superinfection in HBV reactivation

Superinfection is defined as the infection with a second virus or a different strain of virus at a later time point, after the establishment of persistent infection of the first virus[51,58].

Superinfection with HDV of an individual chronically infected with HBV may have deleterious consequences[59]. This pattern of infection causes a severe acute hepatitis that may be self-limited but that in most cases (up to 80%) progresses to chronicity[60]. The resultant chronic HDV infection usually exacerbates the preexisting CHB[60]. It is to be noted that HBV replication is usually suppressed by HDV, and this suppression becomes persistent in the case of a chronic HDV infection[61,62]. Due to concern for HDV superinfection in post-LT setting, it is of utmost importance to prevent HBV recurrence after LT. Nonetheless, patients chronically co-infected with HDV are less at risk of HBV recurrence and have a better survival rate than patients infected with HBV alone. Patients co-infected with HDV generally do not require pre-transplant antiviral therapy due to HBV suppression and low viral load. Although potent HBV DNA-polymerase inhibitors can control HBV replication, reappearance of HBsAg and/or the persistence of HBV DNA in serum, liver, or PBMC might have deleterious consequences in the setting of HBV-HDV co-infection as they may provide the biologic substrate to the reactivation of HDV[40]. No effective antiviral drug is available for the treatment of graft infection with HDV, and potentially the best approach is to keep them on long-term potent antiviral therapy along with low dose of HBIG (Figure 1).

As mentioned before, HBV has ten genotypes named A-J, and they influence the disease outcome and treatment to antiviral therapy[63]. Depending on the geographical location, patients may have one or mixed genotypes of HBV in infected patients and consequences of which possibly have the recombinant HBV genotypes[64-66]. The genotype C of HBV was observed in majority of the HBV-infected patients with acute exacerbation[67]. An earlier published review reported that HBV genotypes D and C are associated with a lower rate of favorable response to alfa-interferon and pegylated-interferon alfa-2b therapy than genotypes A and B[68]. The rate of resistance to lamivudine (LAM) was higher in patients with genotype A infection than in patients infected by genotype D, whereas no difference in the risk of LAM resistance is found between patients
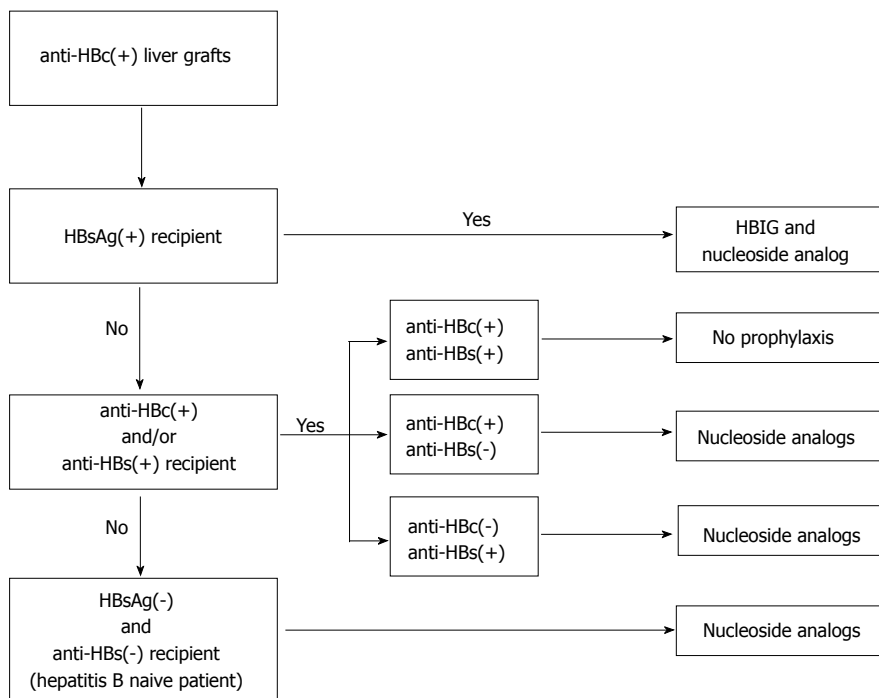
Figure 1 Stepwise approach of anti-hepatitis B core positive grafts allocated to recipients based on their hepatitis B serology. In chronic hepatitis B patients with HBsAg positive and who receive Anti-HBc positive liver grafts should be treated with HBIG and nucleoside analogs. If the recipient is HBsAg negative and Anti-HBc positive and/or anti HBs positive, NA is used for prophylaxis based on anti HBc and anti HBs serologies. No prophylaxis is recommended for anti-HBc positive and anti-HBs positive liver in LT recipient without HBsAg positive serology. These patients should be followed with periodic HBV DNA level guided by ALT to monitor for any relapse. In Hepatitis B naïve patients, NA is recommended for prophylaxis. HBIG: Hepatitis B Immunoglobulin; HBsAg: Hepatitis B surface antigen; Anti-HBs: Hepatitis B surface antibody; Anti-HBc: Hepatitis B core antibody.

with genotype B and patients with genotype C[68]. Later studies using potent nucleotide analogue have shown no genotype specific differences in treatment responses[69]. Another challenge with HBV is the generation of HBV variants through splicing. These variants may get activated with the disease progression post-LT leading to undesirable clinical outcomes as well as the development of drug resistance[70].

Role of HBV integration in HBV reactivation after LT

The role of HBV DNA integration in the genome of host liver cells has been studied from the early 1980s and it had long been postulated to have implications for the antiviral therapy for HBV[71,72]. Recent study demonstrated that HBV can integrate into the host genome immediately after its invasion[73]. HBV DNA integration has been detected in all the stages of HBV infection including occult HBV infection[74]. The potential for oncogenicity has been proven in the woodchuck model with occult WHV infection[75]. In a study from Japan, eighty-two consecutive Japanese patients with cirrhosis, who were negative for serum HBsAg and antibody to hepatitis C virus (anti-HCV) were observed for a median of 5.8 years[76]. The HCC development rates in the patients HBV DNA-positive and HBV DNA-negative were 27.0% and 11.8% at the end of the 5th year, and 100% and 17.6% at the 10th year, respectively.

The clinical significance of occult HBV infection has not been well studied in LT recipients. A recent study investigated the prevalence of occult HBV infection in cirrhotic patients undergoing LT in a Brazilian referral center[77]. Liver samples from 68 adults were analyzed using a nested polymerase chain reaction assay for HBV DNA and occult HBV infection was diagnosed in three (4.4%) patients. Markers of previous HBV infection were available in two patients with occult HBV infection and were negative in both. Clinical impact of occult HBV infection in immunosuppressed individuals has been recently reviewed[78]. These results suggest potential for HBV reactivation post-LT from occult HBV infection. In fact, a recent study with 43 patients with alcoholic cirrhosis, who were negative for serum HBsAg before LT, detectable HBV DNA in the explanted liver was evident in 41.9%[79]. *De novo* HBV infection occurred in 18.6% (8/43) of the recipients at a median of 10 mo after LT.

Extrahepatic replication of HBV and its role in HBV reactivation

Numerous reports demonstrated the presence of HBV DNA, virus genome replicative intermediates and viral proteins in hepatic tissue, and HBV DNA and HBsAg in serum of HBV-infected persons, but the existence of extrahepatic sites of HBV replication are not as well recognized. Nonetheless, the accumulated data indicate that PBMC and different immune cell types can support HBV replication[27,80-83]. Stronger evidence came from the woodchuck model of HBV infection[27,75,84-87]. There are also occasional observations that endothelial cells, epithelial cells, neurons, macrophages and polymorphonuclear leukocytes could be permissive to

HBV infection in humans[88]. HBV replication was also demonstrated in *in vitro* bone marrow cultures and lymphatic tissues of patients with CHB[89-91]. In the woodchuck model of hepatitis B, extrahepatic replication of the woodchuck hepatitis virus and infectivity of the virus derived from lymphoid cells were clearly delineated[75,87]. Interestingly, in some situations, the lymphatic (immune) system might be the only site of virus replication in this model[75,86,87,92].

In one of the xenotransplantation study in patients with baboon liver transplants, Lanford *et al*[93] demonstrated the persistence of HBV DNA in several extrahepatic tissues after HBV replication halted in the liver. In the woodchuck model, the mothers with resident hepadnaviral infection cells transmit the infection to their offspring which is predominantly restricted to their lymphatic system[84]. These observations suggest that the attachment preferences of HBV to cellular receptors on diverse cell types might be responsible for the quasispecies specific compartmentalization of HBV[94]. Studies related to genetic variability, drug resistance and potential immune evasion mechanisms of virus in plasma and PBMC of patients with CHB have also been investigated[95,96]. Because of the diverse nature of the HBV in hepatic and extrahepatic tissues, the response to therapy has been shown to be different in PBMC-restricted HBV compared to hepatic HBV[95]. In these studies, liver, plasma as well as PBMC samples were evaluated using ultrasensitive assays for the quasispecies compatibility in LT patients under long term prophylaxis. The authors inferred that extrahepatic HBV is always detectable in the serum, liver, and PBMC of almost all patients despite prophylaxis, supporting continuation of anti-HBV therapy[95,96]. However, there is not a study yet that demonstrated that reactivation can solely originate from extrahepatic sites.

THE RISK OF HBV REACTIVATION IN LIVER TRANSPLANT PATIENTS UNDERGOING IMMUNOSUPPRESSION THERAPY

Upon HBV entry, the level at which HBV persists depends on the interplay between the viral replication rate and the host immune response. LT patients with prior HBV infection could experience a reactivation of HBV following LT due to immunosuppressive therapy, potentially leading to deleterious consequences, including graft failure and death[97-99].

HBV reactivation in immunosuppressed patients
Immune mechanism: HBV cccDNA and low levels of HBV DNA and RNA remain detectable in host hepatocytes even in patients exposed to HBV who have developed anti-HBs after apparent complete clearance of serum HBsAg and HBV DNA from a recent infection[87,100]. Hence, there seems to be a balance between host HBV-specific T cell and innate immune responses and virus replication that maintains the latency of the viral infection[80,101,102]. Immunosuppressive therapy or cancer chemotherapy may lead to induce imbalance of these mechanisms which causes HBV reactivation[101,103].

Non-immune mechanism: HBV infection can also be flared by steroids[104]. This may include stimulation of a glucocorticoid-responsive element (GRE) in the HBV genome which leads to up regulation of HBV gene expression[105]. In addition, mechanistic target of rapamycin (mTOR) inhibitors, like rapamycin, that are used as immunosuppressive drugs in LT patients and certain cancers, are reported to enhance HBV reactivation in patients[106]. It is also shown that maintaining an immunosuppressive regimen using mTOR-inhibitors post-LT commonly reactivate HBV infection, along with infections with other viruses, such as HCV, cytomegalovirus (CMV), HIV-1, human papilloma virus (HPV), Epstein Barr virus (EBV) and herpes simplex virus (HSV) as well[107].

HCC recurrence after LT
In a Chinese registry study, patients undergoing LT due to HBV-related HCC *vs* HCV-related HCC demonstrated recurrence of HCC at a significantly higher rate in HBV-HCC cohort (26.39%) compared to that in HCV-HCC cohort (9.07%) ($P < 0.001$)[108]. The risk factors for HCC recurrence were: elevated serum alpha fetoprotein, large tumor volume, microvascular invasion, high serum HBV DNA and HBsAg levels, and immunosuppression[109,110].

Younger age has been suggested as a significant risk factor for HBV infection-related HCC recurrence after LT. It has been proposed that this could be due to the vertical transmission of HBV from the occult HBV infection harboring mother and HBV immune tolerant state of the younger patients, triggering HCC recurrence[111,112].

PROPHYLAXIS FOR HBV REACTIVATION AFTER LT

HBsAg-positive patients
Introduction of HBIG in prevention of HBV reactivation following LT was a major milestone. HBIG is pooled polyclonal antibody against HBsAg. Although its mechanism of action remains incompletely understood, it is believed that it prohibits binding of virions to hepatocytes or promotes lysis of infected hepatocytes[113]. In the initial days, prophylaxis for recurrent HBV infection was administered to HBsAg-positive patients using HBIG or LAM monotherapy. This strategy showed significant reduction in re-infection and improvement of graft survival after LT[14,15,114]. Although graft survival was largely improved with either HBIG or LAM monotherapy, the re-infection rates were continued to be 30%-40% of patients[15,19,115]. Furthermore, LAM monotherapy

resulted in development of HBV reverse transcriptase mutations that lead to antiviral drug resistance. When LT patients were on only HBIG prophylactic therapy, their chance of developing HBV escape mutations was significantly higher[116], and this lead to *de novo* HBV infection in some patients after LT[17,117]. First described in 1998, combination therapies of HBIG with NA were successful in controlling HBV infection in most of the patients. None of the 59 patients undergoing LT for HBV-related liver failure who received high dose of HBIG intra- and post-operatively in combination with LAM as prophylaxis, showed detectable HBV DNA after 459 days of treatment[118]. By combining LAM with HBIG, the HBV recurrence rate further dropped to less than 5%. The success of this combination regimen led it to become the most favored antiviral prophylactic regimen in lLT centers worldwide. Despite being effective, HBIG was very expensive and unavailable to a significant percentage of the patient population, and it requires regular parental injections and monitoring. In view of this, lower-dose HBIG in combination with LAM was evaluated and was found to be equally effective[119-121]. However, this combination approach of HBIG with an oral antiviral medication is of historical value only and neither alone was sufficient in preventing HBV reactivation or recurrence. With the availability of newer and more potent oral NA, there has been a shift from HBIG combination therapy to NA alone. A systematic review by Cholongitas *et al*[122] noted a higher recurrence rate with combination of HBIG plus LAM compared to HBIG plus ETV/TDF (6.1% *vs* 1%, *P* = 0.004). A meta-analysis has shown that compared to high dose HBIG-LAM combination, low dose HBIG and potent NAs (TDF or ETV) demonstrated significantly lesser HBV recurrence[123]. Both ETV and TDF have been associated with resistance rate of less than 2% after 5 years in patients with HBV infection[124]. Several earlier studies have demonstrated usefulness of long term HBIG, and more recent studies have demonstrated safe withdrawal of HBIG with continuation of oral antiviral therapies alone by adopting a limited duration of HBIG use in the protocol[119,121,125-138] (Tables 2 and 3).

Hepatitis B core antibody-positive liver donor

LT from hepatitis B core antibody (anti-HBc)-positive donors is being increasingly used due to the shortage of organs. However, due to immunosuppressive therapy, the risk of HBV reactivation is higher after LT in these patients[139]. In a systematic review of 39 studies involving 903 LT patients, Cholongitas *et al*[139] evaluated the risk of HBV recurrence after LT with grafts from anti-HBc-positive donors and effect of anti-HBV prophylaxis. HBV recurrence was found to be 11% in HBsAg-positive LT patients who received anti-HBc-positive grafts compared to anti-HBc-negative grafts, but overall survival was same in both groups. They also noted that *de novo* HBV infection occurred in 19% of HBsAg-negative patients receiving anti-HBc-positive grafts. Without prophylaxis, HBV re-activation

was 15% in anti-HBc/anti-HBs-positive recipients and 48% in HBV naïve patients. However, prophylaxis using HBIG, LAM or a combination decreased re-infection rate significantly. Similarly, *de novo* HBV infection rates in HBsAg-negative patients decreased to 19%, 2.6% and 2.8% using HBIG, LAM and combination, respectively.

This study suggests that anti-HBc positive grafts can be donated safely to HBsAg-positive and anti-HBc/anti-HBs-positive sub groups, and antiviral prophylaxis decreases post-LT reactivation significantly. Due to high risk of reactivation in HBV-naïve patients, anti-HBc-positive grafts should only be considered if other two sub-group recipients are not available[140]. Figure 2 shows stepwise approach in allocating anti-HBc-positive grafts based on recipients HBV serology and prophylaxis after LT.

Anti-HBs and Anti- HBc-positive recipients

De novo HBV infection is substantially lower in anti-HBc and/or anti-HBs-positive compared to HBV-naive recipients[141]. The presence of anti-HBs seems to protect from *de novo* HBV infection and both anti-HBc and anti-HBs-positive recipients represent a group that can safely receive anti-HBc-positive liver grafts without any post-transplant HBV prophylaxis (probability of *de novo* HBV infection < 2%)[142-151]. These patients should however be followed with periodic HBV DNA level guided by ALT to monitor for any relapse. Despite this low risk, many centers prefer to continue with NA without HBIG in this subgroup of patients, and future studies will further clarify this concept (author's personal communication). Figure 3 shows stepwise approach in allocating anti-HBc-positive grafts based on recipients HBV serology and prophylaxis after LT.

Duration of HBIG administration

Currently, there is no consensus regarding the duration of use and dose of HBIG as a component of prophylaxis, and many experts believe in an individualized approach to use of HBIG in prophylaxis[152-154]. A recent study has demonstrated that in HBV-infected patients undergoing LT, who have HBV DNA levels less than 100 U/L and an absence of co-infection with HIV or HDV, a very short course of HBIG in combination with long-term antiviral therapy is highly effective in preventing HBV recurrence[130]. Chen *et al*[131] has shown infusion of two high doses of HBIG during surgery in combination with ETV significantly prevented HBV recurrence and improved the 3-year survival after LY. Another, potential cost saving approach could be combination of ETV plus low-dose on-demand HBIG[155]. Additionally, HBIG-free approach has recently been advocated and is discussed in the later part of this review.

HBIG-free prophylaxis and treatment options

Advent of newer and more-potent NAs with high genetic barrier for resistance such as ETV and TDF, have shown great therapeutic potential as prophylactic agents, and achieved a stronger viral suppression,

Table 2 The results of combination therapy of low-dose hepatitis B immunoglobulin and nucleos(t)ide analogues and the effects of withdrawal of hepatitis B immunoglobulin from combination therapy

Ref.	NA	HBIG protocol	Median follow-up (mo)	HBV recurrence
Angus *et al*[119], 2000	32 LAM	400 IU or 800 IU/d for 1 wk from LT followed by 400 IU or 800 IU/ monthly thereafter	18.4	3.1% HBsAg + and 0% HBV DNA+
Gane *et al*[121], 2007	147 LAM	400 IU or 800 IU/d for 1 wk followed by 400 IU or 800 IU/monthly thereafter	62	1% at 1 yr and 4% at 5 yr. Baseline HBV DNA was associated with HBV recurrence
Karademir *et al*[125], 2006	33 LAM, 2 LAM + ADV	All patients received 4000 IU of intramuscular HBIG during surgery, 2000 IU intramuscular daily thereafter, until the HBsAb titer > 200 IU/mL and the HBsAg was seronegative, followed by lifelong 1200 to 2000 IU HBIG on-demand if HBsAb titer fell below 100 IU/mL	16	5.7% (2 of 35 patients) had HBV DNA recurrence. They were LAM resistant
Iacob *et al*[126], 2008	42 LAM	10000 IU within anhepatic phase and daily within the first postoperative week, followed by 2500 IU on demand	21.6	HBV recurrence rate was 4.8% after a median of 1.8 yr
Jiang *et al*[127], 2010	254 LAM	2000 IU in anhepatic phase, followed by 800 IU/d for first day then weekly for the rest of 3 wk in the first post-operative month, then 800 IU monthly	41.2	1-, 3- and 5-yr HBV recurrence rates were 2.3%, 6.2% and 8.2%, respectively 5 cases have YVDD mutations
Nath *et al*[128], 2006	14 LAM + ADV	1000 IU HBIG in anhepatic phase 1000 IU/daily for week 1, then HBIG withdrawn, replaced with oral ADV	14.1	7.1%
Saab *et al*[129], 2011	18 LAM + HBIG, 16 LAM to LAM + ADV	Randomized trial Patients treated with low dose HBIG + LAM ≥ 1-yr post LT 18 patients continued HBIG 16 patients discontinued HBIG and ADV added	21	0% in HBIG + LMV 6.1% in LMV + ADV Recurrent case: HBsAg + /HBV DNA (-)
Saab *et al*[129], 2011	19 LAM to LAM + ADV, 41 LAM to LAM + TDF, 1 ETV to ETV + ADV	All patients treated with low dose HBIG + LAM ≥ 1-yr post-LT. All patients discontinued HBIG	15	3.3% recurrent cases: HBsAg (+)/ HBV DNA (-)
Radhakrishnan *et al*[130], 2017	42 (ETV (12%), TDF (83%), or TDF/FTC (5%)	HBIG 5000 IU given in anhepatic phase and daily for 5 d together with nucleos(t)ide analogues after LT and then continued indefinitely.	36	1- and 3-year cumulative incidences of recurrence, defined by positive serum HBsAg of 2.9%
Chen *et al*[131], 2015	50 (ETV before and after LT)	Two doses of HBIG-First dose anhepatic phase (10000 IU) and other dose (10000 IU) during surgery (additional doses as needed to maintain HBIG level > 300 IU/mL from 6 wk to 12 mo)	36	0% recurrence at 3 years defined as reappearance of HBsAg and HBV DNA level
Cholangitas *et al*[132], 2016	34 (LAM = 2, AFV = 1, ETV = 9, TDF = 12)	HBIG 1000-10000 IU bolus during anhepatic phase, followed by daily × 7 d, and then monthly 1000-2000 IU intramuscularly for 6-12 mo post-LT and then discontinued NA were continued indefinitely	28	5.8% recurrence defined as reappearance of serum HDV in LT recipients with detectable serum HBsAg and/or HBV DNA
Wesdorp *et al*[133], 2013	17 (15 of 17 converted from LAM/ADV to TDF/FTC)	All received HBIG ± (10000 IU given during anhepatic phase followed by a 4-7 d course of 10000 IU of IV HBIG daily, and then monthly intramuscularly for > 6 mo and then switched to TDF/FTC	24	No recurrence defined by HBsAg and HBV-DNA positivity. However, 6.7% had isolated HBsAg recurrence
Stravitz *et al*[134], 2012	21 (Patients were initially on LAM = 11, ETV = 4, AFV = 2, LAM + ADV = 2, LAM + ADV = 2. All patients were converted to TDF/FTC)	HBIG ± nucleos(t)ide > 6 mo, then substituted with TDF/FTC	31	0% recurrence of HBV DNA after switching to TDF/FTC
Taperman *et al*[135], 2013	37 patients were randomized to TDF/FTC plus HBIG (*n* = 19) or receive (TDF/FTC) alone (*n* = 18)	HBIG ± nucleos(t)ide for 24 wk, then randomized to TDF/FTC plus HBIG (*n* = 19) or receive TDF/FTC alone (*n* = 18) for an additional 72 wk	72	0% recurrence of HBV DNA in both arms

Gane *et al*[136], 2013	20 patients with initial HBIG for 7 d and then switched to LAM+ ADV	HBIG 800 intramuscularly given immediately after LT and the daily for 7 d and then switched to LAM/ ADV	57	0% recurrence defined as reappearance of HBsAg and HBV DNA
McGonigal *et al*[137,141], 2013	4 (ETV = 2, LAM = 1, TDF = 1)	HBIG + NA for more than one year and switched to TDF/FTC	15	0% recurrence of HBsAg and HBV DNA
Angus *et al*[138], 2008	34 patients randomized after 12 mo of HBIG +LAM to ADV (*n* = 16) with and without HIBIG (*n* = 18)	Low dose HBIG × 12 mo along with LAM	4.4 yr for the LAM/ADV and 4.6 yr for the HBIG/LAM group	1 of 15 (6%) in the LAM/ADV and 0 of 15 (0%) in the HBIG/LAM group had HBsAg positive at last follow up

HBIG: Hepatitis B immunoglobulin; HBV: Hepatitis B virus; HBsAg: Hepatitis B surface antigen; HCC: Hepatocellular carcinoma; HIV: Human immunodeficiency virus; HDV: Hepatitis delta virus; LAM: Lamivudine; LT: Liver transplantation; ETV: Entecavir; TDF: Tenofovir.

Table 3 Hepatitis B immunoglobulin-free regimens in preventing recurrence of hepatitis B virus infection after liver transplantation

Ref.	No. of patients	Median duration of follow-up (mo)	Therapy	HBsAg loss	Undetectable HBV DNA
Fung *et al*[161], 2017	265	59	ETV	At 1, 3, 5, and 8 yr of follow up, 85%, 88%, 87.0%, and 92% were negative for HBsAg, respectively	At 1, 3, 5 and 8 yr of follow up, 95%, 99%, 100%, and 100% had undetectable HBV DNA, respectively
Fung *et al*[158], 2013	362	53	LAM = 176 (49%), ETV = 142 (39%), and 44 (12%) were on combination therapy (Either LAM or ETV) plus nucleotide analog (either ADV or TDF)	HBsAg seronegativity at 1, 3, 5 and 8 yr was 80%, 82%, 82% and 88%	HBV DNA suppression to undetectable levels at 1, 3, 5 and 8 yr was 94%, 96%, 96%, and 98%. Rate of HBV DNA suppression for LAM, combination therapy, and ETV at 1 yr was 97%, 94%, and 95%, respectively
Fung *et al*[159], 2011	80	26	ETV	The cumulative rate of HBsAg loss was 86% and 91% after 1 and 2 yr, respectively	95% with undetectable HBV DNA and 5% had low level viremia
Wadhawan *et al*[157], 2013	75	21	19 patients received a combination of LAM+ADV, 42 received entecavir, 12 received TDF, and 2 received a combination of ETV + TDF	The cumulative probabilities of clearing HBsAg were 90% and 92% at 1 and 2 yr after transplantation, respectively	Nine patients were HBsAg-positive with undetectable DNA at the last follow-up. The recurrence rate in our series was 8% (6/75)

HBV: Hepatitis B virus; HBsAg: Hepatitis B surface antigen; LAM: Lamivudine; ETV: Entecavir; TDF: Tenofovir.

paving the way for a HBIG free regimen for antiviral prophylaxis[13,156]. In a multicenter trial by Gane *et al*[136], no HBV recurrence was detected in 28 HBV patients who received a combination of LAM and ADV after a median follow-up of 22 mo when the pre-transplant HBV-DNA level was below 3 log(10) IU/mL. In a later study of 75 HBV patients who received different oral antiviral treatment after LT (19 received a combination of LAM and ADV, 42 ETV, 12 TDF, and 2 received a combination of ETV and TDF), the HBV recurrence rate was merely 8% at a median follow-up of 21 mo and there was no mortality related to HBV recurrence[157]. There was no significant difference in HBsAg clearance and HBV-DNA suppression between those on LAM, combination treatment, or ETV, but virological relapse rate at 3 years was 17%, 7%, and 0%, respectively (*P* < 0.001).

Fung *et al*[158] evaluated monotherapy with NAs (LAM, ETV or LAM plus ADV) without HBIG in a large, long-term cohort study involving 362 LT patients with CHB. At the end of 8 years of follow-up, 98% showed undetectable HBV DNA in serum by clinical assay. Overall 8-year survival rate was 83% with no difference between these three treatment groups and, importantly, no mortality was observed due to HBV recurrence in any of the 362 patients. This study showed that at least in low risk patients, HBIG-free regimen with high potency NAs was safe and effective in preventing post-LT HBV reactivation. For patients without preexisting LAM-resistant mutation, the use of ETV as a standalone treatment remains an ideal choice given its lack of nephrotoxicity. In a study of 80 CHB patients undergoing LT where ETV was used alone in a completely HBIG-free regimen with a median follow-up of 26 mo a high HBsAg seroclearance rate of 86 and 91% after 1 and 2 years respectively was observed[159]. Thirteen percent of patients had HBsAg positivity either from reappearance of HBsAg after initial seroclearance or from persistence of HBsAg-positive status after transplantation. It is important to note that there was no incidence of virological rebound or
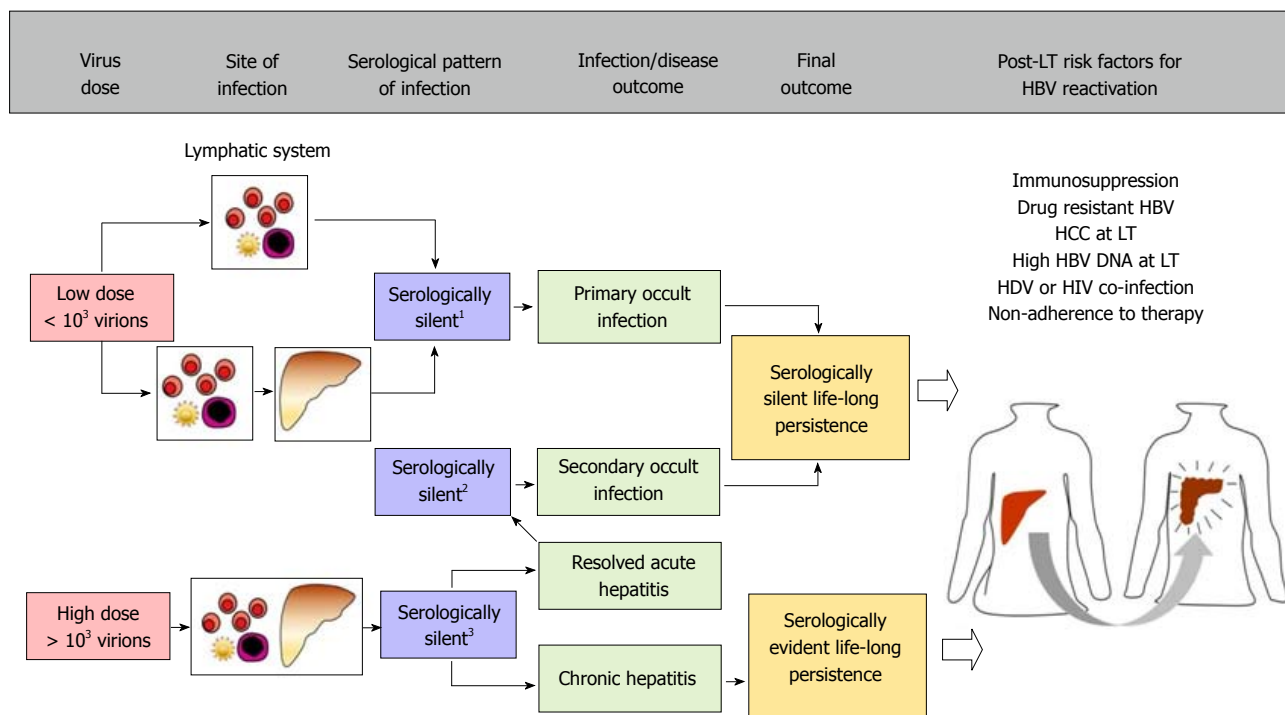
Figure 2 Generalized concept of overt and occult hepatitis B virus infections based on the data from the woodchuck model of hepatitis B, their long-term outcomes, and associated risk factors for hepatitis B virus reactivation following liver transplant. Based on experimental infection in the woodchuck model (Mulrooney-Cousins PM, Michalak TI, 2015[92]). [1]Serologically silent infection: HBsAg, anti-HBc and anti-HBs negative; HBV DNA positive; [2]Serologically silent infection: HBsAg negative, anti-HBc positive, anti-HBs positive or negative; HBV DNA positive; [3]Serologically evident infection: HBsAg and anti-HBc positive, anti-HBs negative. HBV DNA positive. SOI: Secondary occult infection; POI: Primary occult infection; LT: Liver transplant; HCC: Hepatocellular carcinoma; HBV: Hepatitis B virus; HDV: Hepatitis D virus; HBsAg: HBV surface antigen; anti-HBc: Antibodies to HBV core antigen; anti-HBs: Antibodies to HBV surface antigen.

resistance, nor any HBV-related graft hepatitis, graft loss, or mortality. The same group later also followed histological outcomes of CHB patients treated with an HBIG-free regimen, 42 patients were treated with ETV monotherapy who underwent liver biopsies after LT at a median time of 10 mo. Of these, 9 were serum HBsAg-positive at the time of biopsy. All patients were serum HBV DNA-negative- at the time of biopsy. None of these patients had histological evidence of HBV-related graft hepatitis and positive immunohistochemical staining for HBsAg[160]. Fung *et al*[161] also shown the long-term efficacy of using ETV monotherapy in a study involving 165 LT recipients with HBV. The study demonstrated that ETV monotherapy is highly effective at preventing HBV reactivation after LT for CHB, with a durable HBsAg seroclearance rate of 92%, an undetectable HBV DNA rate of 100% at 8 years, and excellent long-term survival of 85% at 9 years.

This approach has been supported by another recent study by Cholngitas *et al*[132]. They have shown that maintenance therapy with NAs prophylaxis after HBIG discontinuation was effective against HBV/HDV recurrence, but it seems that a longer period of HBIG administration might be needed before it is withdrawn after LT. Another large study from Asia has shown long-term ETV monotherapy (without HBIG) is highly effective at preventing HBV reactivation after LT for CHB, with a durable HBsAg seroclearance rate of 92%, an undetectable HBV DNA rate of 100% at 8 years, and

excellent long-term survival of 85% at 9 years. The positive outcomes with the use of ETV monotherapy without HBIG has challenged the need for HBIG post-LT[161] A recent network metanalysis has shown that ETV resulted with the highest probability (31%) as the best prophylactic option on reducing the risk of HBV recurrence. ETV is the preferred oral NAs treatment compared to other five different prophylactic regimens (LAM, TDF, ADV, LAM plus ADV, LAM plus TDF) in the prevention of HBV recurrence after LT[162]. With currently preferred antivirals, namely, those with high barrier to resistance, more patients are likely to have low or undetectable viral load at the time of transplantation and an HBIG-free regimen will more likely be acceptable in the vast majority (Figures 2 and 4). On the other hand, HBIG is still an integral part of prophylaxis in high-risk patients with high pre-transplant HBV DNA level, presence of HCC at LT, co-infection with HIV and HDV, presence of drug-resistance and non-compliance with therapy[152]. However, duration of HBIG in such patients can be guided by testing of serial serum HBV DNA level, and HBsAg status (Figures 2 and 4). A recent study however has challenged this notion, and noted that oral antiviral therapy alone without HBIG is highly effective in preventing reactivation of HBV infection and graft loss from recurrent hepatitis B after LT in patients with preexisting HBV LAM resistance[163]. The cumulative rate of HBsAg seroclearance at 1, 5, and 10 years was 82%, 88%, and 91%, respectively. At the time
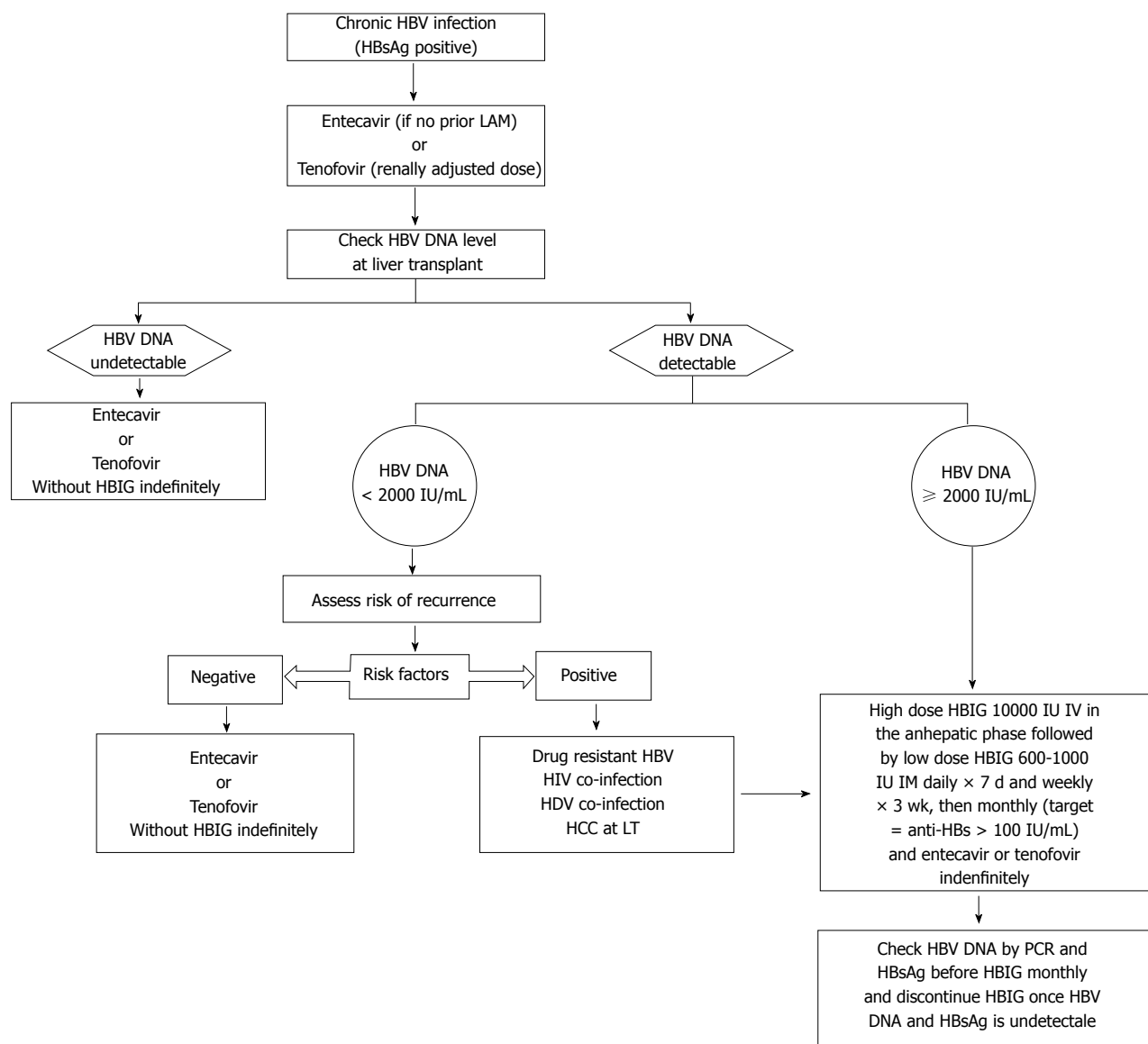
Figure 3 Proposed algorithm for hepatitis B prophylaxis in liver transplant patients. In chronic hepatitis B patients Entecavir (if no prior Lamivudine therapy) or Tenofovir (adjusted to renal function) is recommended as the first line therapy. Based on HBV DNA level at the time of transplant and risk factors, HIBG should be initiated, if associated risk factors for HBV recurrence post LT. High risk patients include drug resistant HBV, HIV co-infection, HDV co-infection, HCC. This group of patients receive high dose IV HBIG 10000 IU given during the anhepatic phase followed by low dose HBIG to achieve target anti HBs > 100 IU/mL along with NAs. HBIG is discontinued once HBV DNA is undetectable and loss of HBsAg is achieved. HBIG: Hepatitis B immunoglobulin; HBV: Hepatitis B virus; HBsAg: Hepatitis B surface antigen; HCC: Hepatocellular carcinoma; HIV: Human immunodeficiency virus; HDV: Hepatitis delta virus; LAM: Lamivudine; LT: Liver transplantation.

of transplantation, 39 (72%) patients had detectable HBV DNA, with a median of 4.5 log copies/mL. The cumulative rate of HBV undetectability was 91% at 1 year, increasing to 100% by 5 years. After 1 year of LT, over 90% of the patients had undetectable HBV DNA, and from 8 years onward, 100% had undetectable HBV DNA in serum. The long-term outcome was excellent, with survival of 87% at 12 years after transplantation, without any mortality related to HBV reactivation. However, HBIG does provide additional benefits beyond preventing HBV recurrence in LT recipients such as its association with reduced rates of rejection[164,165], and modifying risk of developing HCC post-LT[166]. Another important consideration is the potential for preventing graft reinfection such that subsequent discontinuation

of all immunoprophylaxis can be considered[167]. The proposed algorithm for HBV prophylaxis for CHB patients undergoing LT is summarized in Figures 1 and 3.

Complete discontinuation of all prophylaxis
Based on the previous data and clinical studies, lifelong prophylaxis is currently advocated to LT patients to prevent HBV recurrence. Lenci *et al*[167] investigated the safety of withdrawal of prophylactic measures in selected LT patients using a stepwise protocol. The LT patients underwent liver biopsies after receiving a HBIG-LAM combination therapy. It was shown that careful withdrawal of HBIG was safe in patients with undetectable HBV viremia at transplantation and no evidence of total and intrahepatic cccDNA.
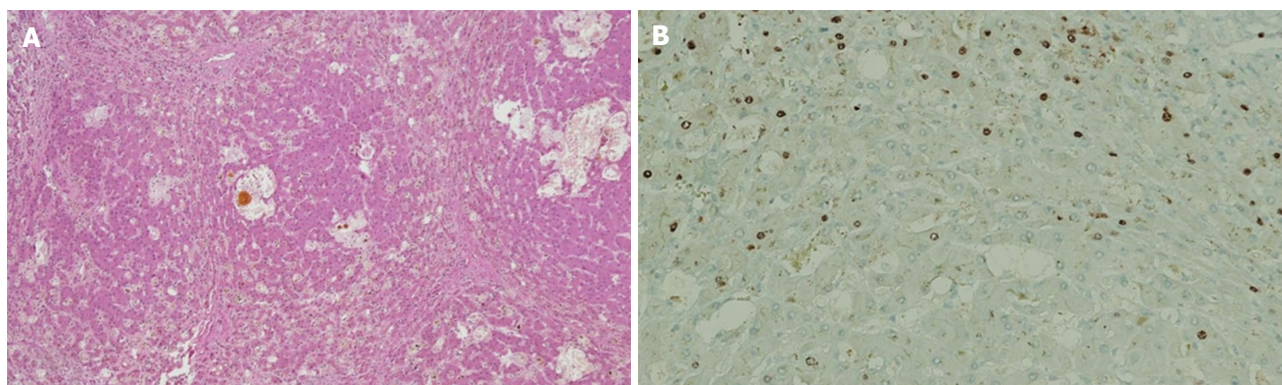
Figure 4 Immunostaining. A: Recurrent hepatitis B virus infection leading to cirrhosis in a post-liver transplantation patient. Figure shows cirrhotic nodules with cholestasis but no appreciable inflammation; B: Immunostaining for hepatitis B core antigen shows strong nuclear accumulation of antigen in a small proportion of hepatocytes indicating active virus propagation.

More recent study showed that complete prophylaxis withdrawal is safe in patients transplanted for HBV-related disease at low risk of recurrence and is often followed by spontaneous anti-HBs seroconversion[168]. However, based on previous studies many centers continue prophylaxis indefinitely as low level HBV viremia is known to persist even after many years of therapy[167,169], and complete discontinuation of all preventative therapy cannot be recommended at this time and should only be performed in the setting of a clinical trial[170].

HBV vaccination and active immunity

Although there is no effective clearance, to ensure a maximum suppression of HBV in LT patients and avoidance of escape mutations caused by long-term administration of HBIG or NAs, it is crucial to develop a strong and long lasting immune response against HBV. Several trials have noted an increase in anti-HBs titer in up to 65% of patients who received HBV vaccination after LT following HBIG withdrawal[141]. More recent study looking at active immunization in *de novo* HBV infection after LT with a HBV core antigen-positive graft have shown that active immunization is effective in preventing *de novo* infection if the post-transplant anti-HBs level is maintained above 100 IU/L with vaccination and antiviral prophylaxis. Prophylaxis can be safely discontinued in this group of patients who obtain this immunity[171].

Emerging therapies and the future of HBV treatment

Current HBV prophylaxis and treatment modalities can only suppress but do not eradicate HBV infection completely; therefore there is a lifelong need for the therapy. Recently, there is a renewed interest to target various stages HBV replication cycle and its interaction with the host.

DAAs and host-targeting agents (HTA) are the two major categories that are being developed and are at various phases of clinical trials[2,13]. Among these, DAAs act by inhibiting viral enzymatic activities or protein function, and generally have excellent safely profile, therefore present an attractive option for drug manufacturers. Major HBV target-specific classes of DAAs that are being developed are inhibitors of cccDNA (*e.g.,* CRISPR/Cas9, sirt1/2, MC2792), hepatocyte entry receptor inhibitors (*via* NTCP; *i.e.,* mycludex, ezetimibe), HBV DNA polymerase inhibitors (HB pol; *e.g.,* GS-7340, besifovir), siRNA target (ARC-520/521), core allosteric modulators (CpAM; *e.g.,* NVR 3-778), immune modulators (*e.g.,* GS9620, nivolumab, pidilizumab), and therapeutic vaccines (*e.g.,* TG-1050)[2,172-177]. These drugs are at various stages of clinical trials and they indicate a promising future for HBV prophylaxis and treatment.

CONCLUSION

With the advent of LT is currently regarded as the ultimate option for treatment for liver cirrhosis, liver failure and HCC associated with chronic HBV infection. Phenomenal success in allograft survival has been achieved by use of HBIG and oral antiviral medications. Prophylaxis with low dose HBIG and oral anti-HBV nucleotides is universally accepted as an effective option to reduce post-transplant viral reactivation. Availability of newer oral anti-HBV nucleos(t)ide analogs (NA), such as ETV and TDF, with higher barriers to resistance and better knowledge of risk factors associated with post-LT HBV reactivation have allowed incorporating these newer NA as part of the antiviral regimen after LT for CHB patients. The use of combination HBIG and lamivudine remains only of historical interest at this time as neither alone was sufficient to prevent HBV recurrence. ETV with its excellent safety profile, low nephrotoxicity, remains the agent of choice for patients without prior lamivudine resistance. For those with prior resistance, the addition of TDF is likely the best treatment option. LT with anti-HBc-positive donors is now possible due to better understanding of the balance between recurrence risk and availability of individualized prophylaxis strategies, and has expanded the pool of donor in an era with high demand for cadaveric donor with scarce supply. Current treatment regimen for

HBV can only control HBV replication, but cannot fully eradicate. As such, efficacy of HBV prophylaxis should be measured by its ability to prevent graft hepatitis and loss secondary to HBV infection, and not in terms of achieving a cure. With currently available potent NA we can achieve substantial suppression of HBV replication, but we are far from achieving viral eradication, although newer antiviral treatments approaches are in development. Hence, a positive HBsAg in post-LT period does not necessarily means HBV recurrence, as the patient has never achieved a virological cure. It is for the same reason we can argue that continuation of HBIG to achieve seroclearance of HBsAg does not achieve any clinical utility as long as viral suppression is achieved with NA. By administering HBIG to keep the antibody titers above a certain arbitrary level, serum HBsAg logically becomes undetectable because of the formation of immune complexes, which evades detection. However, this does not equate to complete eradication, nor the reappearance of serum HBsAg upon stopping HBIG signifies reactivation. In fact, hepatitis B core antigen remains detectable in the liver throughout HBIG administration despite serum HBsAg negativity. As such, long-term prophylaxis with HBIG does not serve any clinical utility and early discontinuation of this practice should be considered as long as complete viral suppression is achieved.

Emerging therapies are now focusing on newer targets of HBV replication and virus-host interaction with an ambitious goal of eradicating HBV infection in the near future rather than mere viral suppression.

ACKNOWLEDGMENTS

REFERENCES

1   **El-Serag HB**. Epidemiology of viral hepatitis and hepatocellular carcinoma. *Gastroenterology* 2012; **142**: 1264-1273.e1 [PMID: 22537432 DOI: 10.1053/j.gastro.2011.12.061]

2   **Durantel D**, Zoulim F. New antiviral targets for innovative treatment concepts for hepatitis B virus and hepatitis delta virus. *J Hepatol* 2016; **64**: S117-S131 [PMID: 27084032 DOI: 10.1016/j.jhep.2016.02.016]

3   **Ryerson AB**, Eheman CR, Altekruse SF, Ward JW, Jemal A, Sherman RL, Henley SJ, Holtzman D, Lake A, Noone AM, Anderson RN, Ma J, Ly KN, Cronin KA, Penberthy L, Kohler BA. Annual Report to the Nation on the Status of Cancer, 1975-2012, featuring the increasing incidence of liver cancer. *Cancer* 2016; **122**: 1312-1337 [PMID: 26959385 DOI: 10.1002/cncr.29936]

4   **Song GW**, Ahn CS, Lee SG, Hwang S, Kim KH, Moon DB, Ha TY, Jung DH, Park GC, Kang SH, Jung BH, Kim N. Correlation between risk of hepatitis B virus recurrence and tissue expression of covalently closed circular DNA in living donor liver transplant recipients treated with high-dose hepatitis B immunoglobulin.

Transplant Proc 2014; **46**: 3548-3553 [PMID: 25498087 DOI: 10.1016/j.transproceed.2014.06.074]

5   **Wu D**, Ning Q. Toward a Cure for Hepatitis B Virus Infection: Combination Therapy Involving Viral Suppression and Immune Modulation and Long-term Outcome. *J Infect Dis* 2017; **216**: S771-S777 [PMID: 29156046 DOI: 10.1093/infdis/jix355]

6   **Sarin SK**, Kumar M, Lau GK, Abbas Z, Chan HL, Chen CJ, Chen DS, Chen HL, Chen PJ, Chien RN, Dokmeci AK, Gane E, Hou JL, Jafri W, Jia J, Kim JH, Lai CL, Lee HC, Lim SG, Liu CJ, Locarnini S, Al Mahtab M, Mohamed R, Omata M, Park J, Piratvisuth T, Sharma BC, Sollano J, Wang FS, Wei L, Yuen MF, Zheng SS, Kao JH. Asian-Pacific clinical practice guidelines on the management of hepatitis B: a 2015 update. *Hepatol Int* 2016; **10**: 1-98 [PMID: 26563120 DOI: 10.1007/s12072-015-9675-4]

7   **Geipel A**, Seiz PL, Niekamp H, Neumann-Fraune M, Zhang K, Kaiser R, Protzer U, Gerlich WH, Glebe D; HOPE Consortium. Entecavir allows an unexpectedly high residual replication of HBV mutants resistant to lamivudine. *Antivir Ther* 2015; **20**: 779-787 [PMID: 25560463 DOI: 10.3851/IMP2928]

8   **Hiramatsu N**, Yamada R, Takehara T. The suppressive effect of nucleos(t)ide analogue treatment on the incidence of hepatocellular carcinoma in chronic hepatitis B patients. *J Gastroenterol Hepatol* 2016; **31**: 546-552 [PMID: 26574149 DOI: 10.1111/jgh.13229]

9   **Michalak TI**. Occult persistence and lymphotropism of hepadnaviral infection: insights from the woodchuck viral hepatitis model. *Immunol Rev* 2000; **174**: 98-111 [PMID: 10807510]

10 **Maier M**, Liebert UG, Wittekind C, Kaiser T, Berg T, Wiegand J. Clinical Relevance of Minimal Residual Viremia during Long-Term Therapy with Nucleos(t)ide Analogues in Patients with Chronic Hepatitis B. *PLoS One* 2013; **8**: e67481 [PMID: 23826307 DOI: 10.1371/journal.pone.0067481]

11 **Moraleda G**, Saputelli J, Aldrich CE, Averett D, Condreay L, Mason WS. Lack of effect of antiviral therapy in nondividing hepatocyte cultures on the closed circular DNA of woodchuck hepatitis virus. *J Virol* 1997; **71**: 9392-9399 [PMID: 9371599]

12 **Nassal M**. HBV cccDNA: viral persistence reservoir and key obstacle for a cure of chronic hepatitis B. *Gut* 2015; **64**: 1972-1984 [PMID: 26048673 DOI: 10.1136/gutjnl-2015-309809]

13 **Zoulim F**, Durantel D. Antiviral therapies and prospects for a cure of chronic hepatitis B. *Cold Spring Harb Perspect Med* 2015; **5**: pii: a021501 [PMID: 25833942 DOI: 10.1101/cshperspect.a021501]

14 **Samuel D**, Bismuth A, Mathieu D, Arulnaden JL, Reynes M, Benhamou JP, Brechot C, Bismuth H. Passive immunoprophylaxis after liver transplantation in HBsAg-positive patients. *Lancet* 1991; **337**: 813-815 [PMID: 1672913]

15 **Samuel D**, Muller R, Alexander G, Fassati L, Ducot B, Benhamou JP, Bismuth H. Liver transplantation in European patients with the hepatitis B surface antigen. *N Engl J Med* 1993; **329**: 1842-1847 [PMID: 8247035 DOI: 10.1056/nejm199312163292503]

16 **Sawyer RG**, McGory RW, Gaffey MJ, McCullough CC, Shephard BL, Houlgrave CW, Ryan TS, Kuhns M, McNamara A, Caldwell SH, Abdulkareem A, Pruett TL. Improved clinical outcomes with liver transplantation for hepatitis B-induced chronic liver failure using passive immunization. *Ann Surg* 1998; **227**: 841-850 [PMID: 9637547]

17 **Faria LC**, Gigou M, Roque-Afonso AM, Sebagh M, Roche B, Fallot G, Ferrari TC, Guettier C, Dussaix E, Castaing D, Brechot C, Samuel D. Hepatocellular carcinoma is associated with an increased risk of hepatitis B virus recurrence after liver transplantation. *Gastroenterology* 2008; **134**: 1890-1899; quiz 2155 [PMID: 18424269 DOI: 10.1053/j.gastro.2008.02.064]

18 **Marzano A**, Gaia S, Ghisetti V, Carenzi S, Premoli A, Debernardi-Venon W, Alessandria C, Franchello A, Salizzoni M, Rizzetto M. Viral load at the time of liver transplantation and risk of hepatitis B virus recurrence. *Liver Transpl* 2005; **11**: 402-409 [PMID: 15776431 DOI: 10.1002/lt.20402]

19 **Mutimer D**, Pillay D, Dragon E, Tang H, Ahmed M, O'Donnell K, Shaw J, Burroughs N, Rand D, Cane P, Martin B, Buchan S, Boxall E, Barmat S, Gutekunst K, McMaster P, Elias E. High pre-treatment serum hepatitis B virus titre predicts failure

of lamivudine prophylaxis and graft re-infection after liver transplantation. *J Hepatol* 1999; **30**: 715-721 [PMID: 10207815]

20   **Coffin CS**, Shaheen AA, Burak KW, Myers RP. Pregnancy outcomes among liver transplant recipients in the United States: a nationwide case-control analysis. *Liver Transpl* 2010; **16**: 56-63 [PMID: 20035524 DOI: 10.1002/lt.21906]

21   **Sarin SK**, Satapathy SK, Chauhan R. Hepatitis B e-antigen negative chronic hepatitis B. *J Gastroenterol Hepatol* 2002; **17** Suppl 3: S311-S321 [PMID: 12472956]

22   **Will H**, Reiser W, Weimer T, Pfaff E, Büscher M, Sprengel R, Cattaneo R, Schaller H. Replication strategy of human hepatitis B virus. *J Virol* 1987; **61**: 904-911 [PMID: 3806799]

23   **Werle-Lapostolle B**, Bowden S, Locarnini S, Wursthorn K, Petersen J, Lau G, Trepo C, Marcellin P, Goodman Z, Delaney WE 4th, Xiong S, Brosgart CL, Chen SS, Gibbs CS, Zoulim F. Persistence of cccDNA during the natural history of chronic hepatitis B and decline during adefovir dipivoxil therapy. *Gastroenterology* 2004; **126**: 1750-1758 [PMID: 15188170]

24   **Wong DK**, Seto WK, Fung J, Ip P, Huang FY, Lai CL, Yuen MF. Reduction of hepatitis B surface antigen and covalently closed circular DNA by nucleos(t)ide analogues of different potency. *Clin Gastroenterol Hepatol* 2013; **11**: 1004-10.e1 [PMID: 23376799 DOI: 10.1016/j.cgh.2013.01.026]

25   **Papatheodoridis GV**, Manolakopoulos S, Touloumi G, Vourli G, Raptopoulou-Gigi M, Vafiadis-Zoumbouli I, Vasiliadis T, Mimidis K, Gogos C, Ketikoglou I, Manesis EK; HEPNET. Greece Cohort Study Group. Virological suppression does not prevent the development of hepatocellular carcinoma in HBeAg-negative chronic hepatitis B patients with cirrhosis receiving oral antiviral(s) starting with lamivudine monotherapy: results of the nationwide HEPNET. Greece cohort study. *Gut* 2011; **60**: 1109-1116 [PMID: 21270118 DOI: 10.1136/gut.2010.221846]

26   **Cheung CK**, Lo CM, Man K, Lau GK. Occult hepatitis B virus infection of donor and recipient origin after liver transplantation despite nucleoside analogue prophylaxis. *Liver Transpl* 2010; **16**: 1314-1323 [PMID: 21031547 DOI: 10.1002/lt.22169]

27   **Coffin CS**, Pham TN, Mulrooney PM, Churchill ND, Michalak TI. Persistence of isolated antibodies to woodchuck hepatitis virus core antigen is indicative of occult infection. *Hepatology* 2004; **40**: 1053-1061 [PMID: 15382154 DOI: 10.1002/hep.20419]

28   **Hoofnagle JH**, Seeff LB, Bales ZB, Zimmerman HJ. Type B hepatitis after transfusion with blood containing antibody to hepatitis B core antigen. *N Engl J Med* 1978; **298**: 1379-1383 [PMID: 652005 DOI: 10.1056/NEJM197806222982502]

29   **Shouval D**. The search for a new endpoint for antiviral prophylaxis in hepatitis B virus transplanted patients. *Dig Liver Dis* 2010; **42**: 537-538 [PMID: 20619822 DOI: 10.1016/j.dld.2010.06.006]

30   **Kay A**, Zoulim F. Hepatitis B virus genetic variability and evolution. *Virus Res* 2007; **127**: 164-176 [PMID: 17383765 DOI: 10.1016/j.virusres.2007.02.021]

31   **Tian Q**, Jia J. Hepatitis B virus genotypes: epidemiological and clinical relevance in Asia. *Hepatol Int* 2016; **10**: 854-860 [PMID: 27300749 DOI: 10.1007/s12072-016-9745-2]

32   **Tanwar S**, Dusheiko G. Is there any value to hepatitis B virus genotype analysis? *Curr Gastroenterol Rep* 2012; **14**: 37-46 [PMID: 22105466 DOI: 10.1007/s11894-011-0233-5]

33   **Wen WH**, Chen HL, Ni YH, Hsu HY, Kao JH, Hu FC, Chang MH. Secular trend of the viral genotype distribution in children with chronic hepatitis B virus infection after universal infant immunization. *Hepatology* 2011; **53**: 429-436 [PMID: 21274864 DOI: 10.1002/hep.24061]

34   **Devarbhavi HC**, Cohen AJ, Patel R, Wiesner RH, Dickson RC, Ishitani MB. Preliminary results: outcome of liver transplantation for hepatitis B virus varies by hepatitis B virus genotype. *Liver Transpl* 2002; **8**: 550-555 [PMID: 12037787 DOI: 10.1053/jlts.2002.33483]

35   **Zöllner B**, Feucht HH, Sterneck M, Schäfer H, Rogiers X, Fischer L. Clinical reactivation after liver transplantation with an unusual minor strain of hepatitis B virus in an occult carrier. *Liver Transpl* 2006; **12**: 1283-1289 [PMID: 16868945 DOI: 10.1002/lt.20858]

36   **Chauhan R**, Singh AK, Rooge S, Varshney A, Kumar M, Sarin

SK. Analysis of hepatitis B virus genotype changes in patients with chronic hepatitis B infection on tenofovir therapy. *J Med Virol* 2016; **88**: 1364-1375 [PMID: 26858138 DOI: 10.1002/jmv.24489]

37   **Buti M**, Tabernero D, Mas A, Homs M, Prieto M, Rodríguez-Frías F, Casafont F, Casillas R, González A, Miras M, Herrero JI, Castells L, Esteban R. Hepatitis B virus quasispecies evolution after liver transplantation in patients under long-term lamivudine prophylaxis with or without hepatitis B immune globulin. *Transpl Infect Dis* 2015; **17**: 208-220 [PMID: 25641570 DOI: 10.1111/tid.12360]

38   **Mina T**, Amini-Bavil-Olyaee S, Dekervel J, Verslype C, Nevens F, Maes P, Tacke F, Van Ranst M, Pourkarim MR. A rare case of HBV genotype fluctuation (shifting and reversion) after liver transplantation. *J Clin Virol* 2015; **71**: 93-97 [PMID: 26342803 DOI: 10.1016/j.jcv.2015.08.010]

39   **Lin JH**, Chang MF, Baker SC, Govindarajan S, Lai MM. Characterization of hepatitis delta antigen: specific binding to hepatitis delta virus RNA. *J Virol* 1990; **64**: 4051-4058 [PMID: 2200884]

40   **Roche B**, Samuel D. Liver transplantation in delta virus infection. *Semin Liver Dis* 2012; **32**: 245-255 [PMID: 22932973 DOI: 10.1055/s-0032-1323630]

41   **Marsman WA**, Wiesner RH, Batts KP, Poterucha JJ, Porayko MK, Niesters HG, Zondervan PE, Krom RA. Fulminant hepatitis B virus: recurrence after liver transplantation in two patients also infected with hepatitis delta virus. *Hepatology* 1997; **25**: 434-438 [PMID: 9021960 DOI: 10.1002/hep.510250230]

42   **Bahde R**, Hölzen JP, Wolters HH, Schmidt HH, Bock CT, Lügering A, Spieker T, Senninger N, Brockmann JG. Course of a HBsAg positive liver transplantation in a hepatitis B and D virus coinfected recipient. *Ann Hepatol* 2011; **10**: 355-360 [PMID: 21677340]

43   **Franchello A**, Ghisetti V, Marzano A, Romagnoli R, Salizzoni M. Transplantation of hepatitis B surface antigen-positive livers into hepatitis B virus-positive recipients and the role of hepatitis delta coinfection. *Liver Transpl* 2005; **11**: 922-928 [PMID: 16035057 DOI: 10.1002/lt.20471]

44   **Lempp FA**, Urban S. Hepatitis Delta Virus: Replication Strategy and Upcoming Therapeutic Options for a Neglected Human Pathogen. *Viruses* 2017; **9**: pii: E172 [PMID: 28677645 DOI: 10.3390/v9070172]

45   **Ottobrelli A**, Marzano A, Smedile A, Recchia S, Salizzoni M, Cornu C, Lamy ME, Otte JB, De Hemptinne B, Geubel A. Patterns of hepatitis delta virus reinfection and disease in liver transplantation. *Gastroenterology* 1991; **101**: 1649-1655 [PMID: 1955130]

46   **Smedile A**, Casey JL, Cote PJ, Durazzo M, Lavezzo B, Purcell RH, Rizzetto M, Gerin JL. Hepatitis D viremia following orthotopic liver transplantation involves a typical HDV virion with a hepatitis B surface antigen envelope. *Hepatology* 1998; **27**: 1723-1729 [PMID: 9620349 DOI: 10.1002/hep.510270636]

47   **Stroffolini T**, Sagnelli E, Sagnelli C, Russello M, De Luca M, Rosina F, Cacopardo B, Brancaccio G, Furlan C, Gaeta GB, Licata A, Almasio PL; behalf of EPACRON study group. Hepatitis delta infection in Italian patients: towards the end of the story? *Infection* 2017; **45**: 277-281 [PMID: 27817147 DOI: 10.1007/s15010-016-0956-1]

48   **Miyaaki H**, Tamada Y, Hayashi K, Taura N, Miuma S, Shibata H, Soyama A, Hidaka M, Takatsuki M, Eguchi S, Nakao K. Recurrent Hepatitis B and D Virus Infection in a Liver Transplant Recipient. *Transplant Proc* 2017; **49**: 175-177 [PMID: 28104130 DOI: 10.1016/j.transproceed.2016.11.010]

49   **Handa H**, Yamaguchi Y. Hepatitis Delta Virus. New York: Springer US, 2007

50   **Taylor JM**. Host RNA circles and the origin of hepatitis delta virus. *World J Gastroenterol* 2014; **20**: 2971-2978 [PMID: 24659888 DOI: 10.3748/wjg.v20.i11.2971]

51   **Negro F**. Hepatitis D Virus Coinfection and Superinfection. *Cold Spring Harb Perspect Med* 2014; **4**: a021550 [PMID: 25368018 DOI: 10.1101/cshperspect.a021550]

52 **Mederacke I**, Filmann N, Yurdaydin C, Bremer B, Puls F, Zacher BJ, Heidrich B, Tillmann HL, Rosenau J, Bock CT, Savas B, Helfritz F, Lehner F, Strassburg CP, Klempnauer J, Wursthorn K, Lehmann U, Manns MP, Herrmann E, Wedemeyer H. Rapid early HDV RNA decline in the peripheral blood but prolonged intrahepatic hepatitis delta antigen persistence after liver transplantation. *J Hepatol* 2012; **56**: 115-122 [PMID: 21762665 DOI: 10.1016/j.jhep.2011.06.016]

53 **David E**, Rahier J, Pucci A, Camby P, Scevens M, Salizzoni M, Otte JB, Galmarini D, Marinucci G, Ottobrelli A. Recurrence of hepatitis D (delta) in liver transplants: histopathological aspects. *Gastroenterology* 1993; **104**: 1122-1128 [PMID: 8462801]

54 **Lucey MR**, Graham DM, Martin P, Di Bisceglie A, Rosenthal S, Waggoner JG, Merion RM, Campbell DA, Nostrant TT, Appelman HD. Recurrence of hepatitis B and delta hepatitis after orthotopic liver transplantation. *Gut* 1992; **33**: 1390-1396 [PMID: 1446866]

55 **Adil B**, Fatih O, Volkan I, Bora B, Veysel E, Koray K, Cemalettin K, Burak I, Sezai Y. Hepatitis B Virus and Hepatitis D Virus Recurrence in Patients Undergoing Liver Transplantation for Hepatitis B Virus and Hepatitis B Virus Plus Hepatitis D Virus. *Transplant Proc* 2016; **48**: 2119-2123 [PMID: 27569956 DOI: 10.1016/j.transproceed.2016.02.076]

56 **Jiang Z**, Feng X, Zhang W, Gao F, Ling Q, Zhou L, Xie H, Chen Q, Zheng S. Recipient cytotoxic T lymphocyte antigen -4+ 49 G/G genotype is associated with reduced incidence of hepatitis B virus recurrence after liver transplantation among Chinese patients. *Liver Int* 2007; **27:** 1202-1208 [PMID: 17919231 DOI: 10.1111/j.1478-3231.2007.01553.x]

57 **Thio CL**, Mosbruger TL, Kaslow RA, Karp CL, Strathdee SA, Vlahov D, O'Brien SJ, Astemborski J, Thomas DL. Cytotoxic T-lymphocyte antigen 4 gene and recovery from hepatitis B virus infection. *J Virol* 2004; **78:** 11258-11262 [PMID: 15452244 DOI: 10.1128/JVI.78.20.11258-11262.2004]

58 **Liaw YF**, Yeh CT, Tsai SL. Impact of acute hepatitis B virus superinfection on chronic hepatitis C virus infection. *Am J Gastroenterol* 2000; **95**: 2978-2980 [PMID: 11051381 DOI: 10.1111/j.1572-0241.2000.02337.x]

59 **Couto I**, Victoria M, Veloso VG, Rodrigues L, Grinsztejn B, Lacerda M, Victoria F, Perazzo H. Prevalence and predictors for compensated Advanced Chronic Liver Disease (c-ACLD) in patients with chronic Hepatitis Delta Virus (HDV) infection. *PLoS One* 2017; **12**: e0174453 [PMID: 28329027 DOI: 10.1371/journal.pone.0174453]

60 **Smedile A**, Farci P, Verme G, Caredda F, Cargnel A, Caporaso N, Dentico P, Trepo C, Opolon P, Gimson A, Vergani D, Williams R, Rizzetto M. Influence of delta infection on severity of hepatitis B. *Lancet* 1982; **2**: 945-947 [PMID: 6127458]

61 **Krogsgaard K**, Kryger P, Aldershvile J, Andersson P, Sørensen TI, Nielsen JO. Delta-infection and suppression of hepatitis B virus replication in chronic HBsAg carriers. *Hepatology* 1987; **7**: 42-45 [PMID: 3804204]

62 **Farci P**, Karayiannis P, Lai ME, Marongiu F, Orgiana G, Balestrieri A, Thomas HC. Acute and chronic hepatitis delta virus infection: direct or indirect effect on hepatitis B virus replication? *J Med Virol* 1988; **26**: 279-288 [PMID: 3204366]

63 **Rajoriya N**, Combet C, Zoulim F, Janssen HLA. How viral genetic variants and genotypes influence disease and treatment outcome of chronic hepatitis B. Time for an individualised approach? *J Hepatol* 2017; **67**: 1281-1297 [PMID: 28736138 DOI: 10.1016/j.jhep.2017.07.011]

64 **Araujo NM.** Hepatitis B virus intergenotypic recombinants worldwide: an overview. *Infect Genet Evol* 2015; **36**: 500-510 [PMID: 26299884 DOI: 10.1016/j.meegid.2015.08.024]

65 **Sy BT**, Nguyen HM, Toan NL, Song LH, Tong HV, Wolboldt C, Binh VQ, Kremsner PG, Velavan TP, Bock CT. Identification of a natural intergenotypic recombinant hepatitis delta virus genotype 1 and 2 in Vietnamese HBsAg-positive patients. *J Viral Hepat* 2015; **22**: 55-63 [PMID: 24548489 DOI: 10.1111/jvh.12228]

66 **Chauhan R**, Kazim SN, Kumar M, Bhattacharjee J, Krishnamoorthy N, Sarin SK. Identification and characterization of genotype A and D recombinant hepatitis B virus from Indian chronic HBV isolates. *World J Gastroenterol* 2008; **14**: 6228-6236 [PMID: 18985816 DOI: 10.3748/wjg.14.6228]

67 **Kao JH**, Chen PJ, Lai MY, Chen DS. Acute exacerbations of chronic hepatitis B are rarely associated with superinfection of hepatitis B virus. *Hepatology* 2001; **34**: 817-823 [PMID: 11584381 DOI: 10.1053/jhep.2001.28188]

68 **Palumbo E**. Hepatitis B genotypes and response to antiviral therapy: a review. *Am J Ther* 2007; **14**: 306-309 [PMID: 17515708 DOI: 10.1097/01.pap.0000249927.67907.eb]

69 **Kim DY**, Kim HJ, Lee CK, Suh JH, Kim DH, Cho YS, Won SY, Park BK, Park IS. Efficacy of adefovir dipivoxil in the treatment of lamivudine-resistant hepatitis B virus genotype C infection. *Liver Int* 2007; **27**: 47-53 [PMID: 17241380 DOI: 10.1111/j.1478-3231.2006.01407.x]

70 **Betz-Stablein B**, Töpfer A, Littlejohn M, Yuen L, Colledge D, Sozzi V, Angus P, Thompson A, Revill P, Beerenwinkel N. Single-molecule sequencing reveals complex genome variation of hepatitis B virus during 15 years of chronic infection following liver transplantation. *J Virol* 2016; **90:** 7171-7183 [PMID: 27252524 DOI: 10.1128/JVI.00243-16]

71 **Brechot C**, Pourcel C, Louise A, Rain B, Tiollais P. Presence of integrated hepatitis B virus DNA sequences in cellular DNA of human hepatocellular carcinoma. *Nature* 1980; **286**: 533-535 [PMID: 6250074]

72 **Bréchot C**, Hadchouel M, Scotto J, Fonck M, Potet F, Vyas GN, Tiollais P. State of hepatitis B virus DNA in hepatocytes of patients with hepatitis B surface antigen-positive and -negative liver diseases. *Proc Natl Acad Sci USA* 1981; **78**: 3906-3910 [PMID: 6267609]

73 **Chauhan R**, Churchill ND, Mulrooney-Cousins PM, Michalak TI. Initial sites of hepadnavirus integration into host genome in human hepatocytes and in the woodchuck model of hepatitis B-associated hepatocellular carcinoma. *Oncogenesis* 2017; **6**: e317 [PMID: 28414318 DOI: 10.1038/oncsis.2017.22]

74 **Saitta C**, Tripodi G, Barbera A, Bertuccio A, Smedile A, Ciancio A, Raffa G, Sangiovanni A, Navarra G, Raimondo G, Pollicino T. Hepatitis B virus (HBV) DNA integration in patients with occult HBV infection and hepatocellular carcinoma. *Liver Int* 2015; **35**: 2311-2317 [PMID: 25677098 DOI: 10.1111/liv.12807]

75 **Mulrooney-Cousins PM**, Chauhan R, Churchill ND, Michalak TI. Primary seronegative but molecularly evident hepadnaviral infection engages liver and induces hepatocarcinoma in the woodchuck model of hepatitis B. *PLoS Pathog* 2014; **10**: e1004332 [PMID: 25165821 DOI: 10.1371/journal.ppat.1004332]

76 **Ikeda K**, Kobayashi M, Someya T, Saitoh S, Hosaka T, Akuta N, Suzuki F, Suzuki Y, Arase Y, Kumada H. Occult hepatitis B virus infection increases hepatocellular carcinogenesis by eight times in patients with non-B, non-C liver cirrhosis: a cohort study. *J Viral Hepat* 2009; **16**: 437-443 [PMID: 19226331 DOI: 10.1111/j.1365-2893.2009.01085.x]

77 **Ferrari TC**, Xavier MA, Vidigal PV, Amaral NS, Diniz PA, Resende AP, Miranda DM, Faria AC, Lima AS, Faria LC. Occult hepatitis B virus infection in liver transplant patients in a Brazilian referral center. *Braz J Med Biol Res* 2014; **47**: 990-994 [PMID: 25296362]

78 **Sagnelli E**, Pisaturo M, Martini S, Filippini P, Sagnelli C, Coppola N. Clinical impact of occult hepatitis B virus infection in immunosuppressed patients. *World J Hepatol* 2014; **6**: 384-393 [PMID: 25018849 DOI: 10.4254/wjh.v6.i6.384]

79 **Xie M**, Rao W, Yang T, Deng Y, Zheng H, Pan C, Liu Y, Shen Z, Jia J. Occult hepatitis B virus infection predicts de novo hepatitis B infection in patients with alcoholic cirrhosis after liver transplantation. *Liver Int* 2015; **35**: 897-904 [PMID: 24750566 DOI: 10.1111/liv.12567]

80 **Marusawa H**, Uemoto S, Hijikata M, Ueda Y, Tanaka K, Shimotohno K, Chiba T. Latent hepatitis B virus infection in healthy individuals with antibodies to hepatitis B core antigen. *Hepatology* 2000; **31**: 488-495 [PMID: 10655275 DOI: 10.1002/hep.510310232]

81 **Pontisso P**, Poon MC, Tiollais P, Brechot C. Detection of hepatitis B virus DNA in mononuclear blood cells. *Br Med J* (Clin Res Ed) 1984; **288**: 1563-1566 [PMID: 6426645]

82 **Bouffard P**, Lamelin JP, Zoulim F, Pichoud C, Trepo C. Different forms of hepatitis B virus DNA and expression of HBV antigens in peripheral blood mononuclear cells in chronic hepatitis B. *J Med Virol* 1990; **31**: 312-317 [PMID: 2269882]

83 **Mason A**, Wick M, White H, Perrillo R. Hepatitis B virus replication in diverse cell types during chronic hepatitis B virus infection. *Hepatology* 1993; **18**: 781-789 [PMID: 8406351]

84 **Coffin CS**, Michalak TI. Persistence of infectious hepadnavirus in the offspring of woodchuck mothers recovered from viral hepatitis. *J Clin Invest* 1999; **104**: 203-212 [PMID: 10411550 DOI: 10.1172/JCI5048]

85 **Michalak TI**, Pardoe IU, Coffin CS, Churchill ND, Freake DS, Smith P, Trelegan CL. Occult lifelong persistence of infectious hepadnavirus and residual liver inflammation in woodchucks convalescent from acute viral hepatitis. *Hepatology* 1999; **29**: 928-938 [PMID: 10051500 DOI: 10.1002/hep.510290329]

86 **Michalak TI**, Mulrooney PM, Coffin CS. Low doses of hepadnavirus induce infection of the lymphatic system that does not engage the liver. *J Virol* 2004; **78**: 1730-1738 [PMID: 14747538]

87 **Ogston CW**, Schechter EM, Humes CA, Pranikoff MB. Extrahepatic replication of woodchuck hepatitis virus in chronic infection. *Virology* 1989; **169**: 9-14 [PMID: 2922930]

88 **Dejean A**, Lugassy C, Zafrani S, Tiollais P, Brechot C. Detection of hepatitis B virus DNA in pancreas, kidney and skin of two human carriers of the virus. *J Gen Virol* 1984; **65** (Pt 3): 651-655 [PMID: 6699625 DOI: 10.1099/0022-1317-65-3-651]

89 **Romet-Lemonne JL**, McLane MF, Elfassi E, Haseltine WA, Azocar J, Essex M. Hepatitis B virus infection in cultured human lymphoblastoid cells. *Science* 1983; **221**: 667-669 [PMID: 6867736]

90 **Elfassi E**, Romet-Lemonne JL, Essex M, Frances-McLane M, Haseltine WA. Evidence of extrachromosomal forms of hepatitis B viral DNA in a bone marrow culture obtained from a patient recently infected with hepatitis B virus. *Proc Natl Acad Sci USA* 1984; **81**: 3526-3528 [PMID: 6587366]

91 **Umeda M**, Marusawa H, Seno H, Katsurada A, Nabeshima M, Egawa H, Uemoto S, Inomata Y, Tanaka K, Chiba T. Hepatitis B virus infection in lymphatic tissues in inactive hepatitis B carriers. *J Hepatol* 2005; **42**: 806-812 [PMID: 15885350 DOI: 10.1016/j.jhep.2005.01.016]

92 **Mulrooney-Cousins PM**, Michalak TI. Asymptomatic Hepadnaviral Persistence and Its Consequences in the Woodchuck Model of Occult Hepatitis B Virus Infection. *J Clin Transl Hepatol* 2015; **3**: 211-219 [PMID: 26623268 DOI: 10.14218/JCTH.2015.00020]

93 **Lanford RE**, Michaels MG, Chavez D, Brasky K, Fung J, Starzl TE. Persistence of extrahepatic hepatitis B virus DNA in the absence of detectable hepatic replication in patients with baboon liver transplants. *J Med Virol* 1995; **46**: 207-212 [PMID: 7561791]

94 **Gao S**, Duan ZP, Chen Y, van der Meer F, Lee SS, Osiowy C, van Marle G, Coffin CS. Compartmental HBV evolution and replication in liver and extrahepatic sites after nucleos/tide analogue therapy in chronic hepatitis B carriers. *J Clin Virol* 2017; **94**: 8-14 [PMID: 28709006 DOI: 10.1016/j.jcv.2017.06.009]

95 **Coffin CS**, Mulrooney-Cousins PM, Peters MG, van Marle G, Roberts JP, Michalak TI, Terrault NA. Molecular characterization of intrahepatic and extrahepatic hepatitis B virus (HBV) reservoirs in patients on suppressive antiviral therapy. *J Viral Hepat* 2011; **18**: 415-423 [PMID: 20626626 DOI: 10.1111/j.1365-2893.2010.01321.x]

96 **Coffin CS**, Mulrooney-Cousins PM, van Marle G, Roberts JP, Michalak TI, Terrault NA. Hepatitis B virus quasispecies in hepatic and extrahepatic viral reservoirs in liver transplant recipients on prophylactic therapy. *Liver Transpl* 2011; **17**: 955-962 [PMID: 21462295 DOI: 10.1002/lt.22312]

97 **Gish RG**, McCashland T. Hepatitis B in liver transplant recipients. *Liver Transpl* 2006; **12**: S54-S64 [PMID: 17051551 DOI: 10.1002/lt.20950]

98 **Kubo S**, Nishiguchi S, Hamba H, Hirohashi K, Tanaka H, Shuto T, Kinoshita H, Kuroki T. Reactivation of viral replication after liver resection in patients infected with hepatitis B virus. *Ann Surg* 2001; **233**: 139-145 [PMID: 11141236]

99 **Perrillo RP**, Gish R, Falck-Ytter YT. American Gastroenterological Association Institute technical review on prevention and treatment of hepatitis B virus reactivation during immunosuppressive drug therapy. *Gastroenterology* 2015; **148**: 221-244.e3 [PMID: 25447852 DOI: 10.1053/j.gastro.2014.10.038]

100 **Yang HC**, Kao JH. Persistence of hepatitis B virus covalently closed circular DNA in hepatocytes: molecular mechanisms and clinical significance. *Emerg Microbes Infect* 2014; **3**: e64 [PMID: 26038757 DOI: 10.1038/emi.2014.64]

101 **Raimondo G**, Allain JP, Brunetto MR, Buendia MA, Chen DS, Colombo M, Craxì A, Donato F, Ferrari C, Gaeta GB, Gerlich WH, Levrero M, Locarnini S, Michalak T, Mondelli MU, Pawlotsky JM, Pollicino T, Prati D, Puoti M, Samuel D, Shouval D, Smedile A, Squadrito G, Trépo C, Villa E, Will H, Zanetti AR, Zoulim F. Statements from the Taormina expert meeting on occult hepatitis B virus infection. *J Hepatol* 2008; **49**: 652-657 [PMID: 18715666 DOI: 10.1016/j.jhep.2008.07.014]

102 **Michalak TI**, Pasquinelli C, Guilhot S, Chisari FV. Hepatitis B virus persistence after recovery from acute viral hepatitis. *J Clin Invest* 1994; **94**: 907 [PMID: 8040346]

103 **Oh MJ**, Lee HJ. A study of hepatitis B virus reactivation associated with rituximab therapy in real-world clinical practice: a single-center experience. *Clin Mol Hepatol* 2013; **19**: 51-59 [PMID: 23593610 DOI: 10.3350/cmh.2013.19.1.51]

104 **Jhuang HJ**, Hsu WH, Lin KT, Hsu SL, Wang FS, Chou CK, Lee KH, Tsou AP, Lai JM, Yeh SF, Huang CY. Gluconeogenesis, lipogenesis, and HBV replication are commonly regulated by PGC-1α-dependent pathway. *Oncotarget* 2015; **6**: 7788-7803 [PMID: 25762623 DOI: 10.18632/oncotarget.3050]

105 **Tur-Kaspa R**, Shaul Y, Moore DD, Burk RD, Okret S, Poellinger L, Shafritz DA. The glucocorticoid receptor recognizes a specific nucleotide sequence in hepatitis B virus DNA causing increased activity of the HBV enhancer. *Virology* 1988; **167**: 630-633 [PMID: 3201757]

106 **Huang W**, Zhao F, Huang Y, Li X, Zhu S, Hu Q, Chen W. Rapamycin enhances HBV production by inducing cellular autophagy. *Hepat Mon* 2014; **14**: e20719 [PMID: 25419217 DOI: 10.5812/hepatmon.20719]

107 **Brennan DC**, Aguado JM, Potena L, Jardine AG, Legendre C, Säemann MD, Mueller NJ, Merville P, Emery V, Nashan B. Effect of maintenance immunosuppressive drugs on virus pathobiology: evidence and potential mechanisms. *Rev Med Virol* 2013; **23**: 97-125 [PMID: 23165654 DOI: 10.1002/rmv.1733]

108 **Hu Z**, Zhou J, Wang H, Zhang M, Li S, Huang Y, Wu J, Li Z, Zhou L, Zheng S. Survival in liver transplant recipients with hepatitis B- or hepatitis C-associated hepatocellular carcinoma: the Chinese experience from 1999 to 2010. *PLoS One* 2013; **8**: e61620 [PMID: 23613886 DOI: 10.1371/journal.pone.0061620]

109 **Huang G**, Lau WY, Zhou WP, Shen F, Pan ZY, Yuan SX, Wu MC. Prediction of Hepatocellular Carcinoma Recurrence in Patients With Low Hepatitis B Virus DNA Levels and High Preoperative Hepatitis B Surface Antigen Levels. *JAMA Surg* 2014; **149**: 519-527 [PMID: 24696192 DOI: 10.1001/jamasurg.2013.4648]

110 **Marelli L**, Grasso A, Pleguezuelo M, Martines H, Stigliano R, Dhillon AP, Patch D, Davidson BR, Sharma D, Rolles K, Burroughs AK. Tumour size and differentiation in predicting recurrence of hepatocellular carcinoma after liver transplantation: external validation of a new prognostic score. *Ann Surg Oncol* 2008; **15**: 3503-3511 [PMID: 18777193 DOI: 10.1245/s10434-008-0128-3]

111 **Wai CT**, Woon WA, Tan YM, Lee KH, Tan KC. Younger age and presence of macrovascular invasion were independent significant factors associated with poor disease-free survival in hepatocellular carcinoma patients undergoing living donor liver transplantation. *Transplant Proc* 2012; **44**: 516-519 [PMID: 22410059 DOI: 10.1016/j.transproceed.2012.01.032]

112 **Bertuzzo VR**, Cescon M, Ravaioli M, Grazi GL, Ercolani G, Del Gaudio M, Cucchetti A, D'Errico-Grigioni A, Golfieri R, Pinna

AD. Analysis of factors affecting recurrence of hepatocellular carcinoma after liver transplantation with a special focus on inflammation markers. *Transplantation* 2011; **91**: 1279-1285 [PMID: 21617590 DOI: 10.1097/TP.0b013e3182187cf0]

113 **Celis E**, Abraham KG, Miller RW. Modulation of the immunological response to hepatitis B virus by antibodies. *Hepatology* 1987; **7**: 563-568 [PMID: 3494654]

114 **Müller R**, Gubernatis G, Farle M, Niehoff G, Klein H, Wittekind C, Tusch G, Lautz HU, Böker K, Stangel W. Liver transplantation in HBs antigen (HBsAg) carriers. Prevention of hepatitis B virus (HBV) recurrence by passive immunization. *J Hepatol* 1991; **13**: 90-96 [PMID: 1918881]

115 **Perrillo RP**, Wright T, Rakela J, Levy G, Schiff E, Gish R, Martin P, Dienstag J, Adams P, Dickson R, Anschuetz G, Bell S, Condreay L, Brown N; Lamivudine North American Transplant Group. A multicenter United States-Canadian trial to assess lamivudine monotherapy before and after liver transplantation for chronic hepatitis B. *Hepatology* 2001; **33**: 424-432 [PMID: 11172345 DOI: 10.1053/jhep.2001.21554]

116 **Roche B**, Roque-Afonso AM, Sebagh M, Delvart V, Duclos-Vallee JC, Castaing D, Samuel D. Escape hepatitis B virus mutations in recipients of antibody to hepatitis B core antigen-positive liver grafts receiving hepatitis B immunoglobulins. *Liver Transpl* 2010; **16**: 885-894 [PMID: 20583085 DOI: 10.1002/lt.22084]

117 **Ueda Y**, Marusawa H, Egawa H, Okamoto S, Ogura Y, Oike F, Nishijima N, Takada Y, Uemoto S, Chiba T. De novo activation of HBV with escape mutations from hepatitis B surface antibody after living donor liver transplantation. *Antivir Ther* 2011; **16**: 479-487 [PMID: 21685535 DOI: 10.3851/imp1771]

118 **Lok AS**. Prevention of recurrent hepatitis B post-liver transplantation. *Liver Transpl* 2002; **8**: S67-S73 [PMID: 12362302 DOI: 10.1053/jlts.2002.35780]

119 **Angus PW**, McCaughan GW, Gane EJ, Crawford DH, Harley H. Combination low-dose hepatitis B immune globulin and lamivudine therapy provides effective prophylaxis against posttransplantation hepatitis B. *Liver Transpl* 2000; **6**: 429-433 [PMID: 10915163 DOI: 10.1053/jlts.2000.8310]

120 **Markowitz JS**, Martin P, Conrad AJ, Markmann JF, Seu P, Yersiz H, Goss JA, Schmidt P, Pakrasi A, Artinian L, Murray NG, Imagawa DK, Holt C, Goldstein LI, Stribling R, Busuttil RW. Prophylaxis against hepatitis B recurrence following liver transplantation using combination lamivudine and hepatitis B immune globulin. *Hepatology* 1998; **28**: 585-589 [PMID: 9696028 DOI: 10.1002/hep.510280241]

121 **Gane EJ**, Angus PW, Strasser S, Crawford DH, Ring J, Jeffrey GP, McCaughan GW; Australasian Liver Transplant Study Group. Lamivudine plus low-dose hepatitis B immunoglobulin to prevent recurrent hepatitis B following liver transplantation. *Gastroenterology* 2007; **132**: 931-937 [PMID: 17383422 DOI: 10.1053/j.gastro.2007.01.005]

122 **Cholongitas E**, Papatheodoridis GV. High genetic barrier nucleos(t)ide analogue(s) for prophylaxis from hepatitis B virus recurrence after liver transplantation: a systematic review. *Am J Transplant* 2013; **13**: 353-362 [PMID: 23137006 DOI: 10.1111/j.1600-6143.2012.04315.x]

123 **Katz LH**, Paul M, Guy DG, Tur-Kaspa R. Prevention of recurrent hepatitis B virus infection after liver transplantation: hepatitis B immunoglobulin, antiviral drugs, or both? Systematic review and meta-analysis. *Transpl Infect Dis* 2010; **12**: 292-308 [PMID: 20002355 DOI: 10.1111/j.1399-3062.2009.00470.x]

124 **Chang TT**, Lai CL, Kew Yoon S, Lee SS, Coelho HS, Carrilho FJ, Poordad F, Halota W, Horsmans Y, Tsai N, Zhang H, Tenney DJ, Tamez R, Iloeje U. Entecavir treatment for up to 5 years in patients with hepatitis B e antigen-positive chronic hepatitis B. *Hepatology* 2010; **51**: 422-430 [PMID: 20049753 DOI: 10.1002/hep.23327]

125 **Karademir S**, Astarcioğlu H, Akarsu M, Ozkardesler S, Ozzeybek D, Sayiner A, Akan M, Tankurt E, Astarcioğlu I. Prophylactic use of low-dose, on-demand, intramuscular hepatitis B immunoglobulin and lamivudine after liver transplantation. *Transplant Proc* 2006; **38**: 579-583 [PMID: 16549180 DOI: 10.1016/j.transproceed.2005.

12.063]

126 **Iacob S**, Hrehoret D, Matei E, Dorobantu B, Gangone E, Gheorghe L, Popescu I. Costs and efficacy of "on demand" low-dose immunoprophylaxis in HBV transplanted patients: experience in the Romanian program of liver transplantation. *J Gastrointestin Liver Dis* 2008; **17**: 383-388 [PMID: 19104697]

127 **Jiang L**, Yan L, Li B, Wen T, Zhao J, Jiang L, Cheng N, Wei Y, Yang J, Xu M, Wang W. Prophylaxis against hepatitis B recurrence posttransplantation using lamivudine and individualized low-dose hepatitis B immunoglobulin. *Am J Transplant* 2010; **10**: 1861-1869 [PMID: 20659092 DOI: 10.1111/j.1600-6143.2010.03208.x]

128 **Nath DS**, Kalis A, Nelson S, Payne WD, Lake JR, Humar A. Hepatitis B prophylaxis post-liver transplant without maintenance hepatitis B immunoglobulin therapy. *Clin Transplant* 2006; **20**: 206-210 [PMID: 16640528 DOI: 10.1111/j.1399-0012.2005.00467.x]

129 **Saab S**, Desai S, Tsaoi D, Durazo F, Han S, McClune A, Holt C, Farmer D, Goldstein L, Busuttil RW. Posttransplantation hepatitis B prophylaxis with combination oral nucleoside and nucleotide analog therapy. *Am J Transplant* 2011; **11**: 511-517 [PMID: 21299826 DOI: 10.1111/j.1600-6143.2010.03416.x]

130 **Radhakrishnan K**, Chi A, Quan DJ, Roberts JP, Terrault NA. Short Course of Postoperative Hepatitis B Immunoglobulin Plus Antivirals Prevents Reinfection of Liver Transplant Recipients. *Transplantation* 2017; **101**: 2079-2082 [PMID: 28880197 DOI: 10.1097/TP.0000000000001786]

131 **Chen G**, Liu H, Hu ZQ, Bai JH, Liu QY, Zhao YP, Gan XM, Wang F, Wang DD, Ma LJ, Li L. A new scheme with infusion of hepatitis B immunoglobulin combined with entecavir for prophylaxis of hepatitis B virus recurrence among liver transplant recipients. *Eur J Gastroenterol Hepatol* 2015; **27**: 901-906 [PMID: 26011237 DOI: 10.1097/meg.0000000000000388]

132 **Cholongitas E**, Goulis I, Antoniadis N, Fouzas I, Imvrios G, Giakoustidis D, Giouleme O, Papanikolaou V, Akriviadis E, Vasiliadis T. Nucleos(t)ide analog(s) prophylaxis after hepatitis B immunoglobulin withdrawal against hepatitis B and D recurrence after liver transplantation. *Transpl Infect Dis* 2016; **18**: 667-673 [PMID: 27421122 DOI: 10.1111/tid.12575]

133 **Wesdorp DJ**, Knoester M, Braat AE, Coenraad MJ, Vossen AC, Claas EC, van Hoek B. Nucleoside plus nucleotide analogs and cessation of hepatitis B immunoglobulin after liver transplantation in chronic hepatitis B is safe and effective. *J Clin Virol* 2013; **58**: 67-73 [PMID: 23880162 DOI: 10.1016/j.jcv.2013.06.035]

134 **Stravitz RT**, Shiffman ML, Kimmel M, Puri P, Luketic VA, Sterling RK, Sanyal AJ, Cotterell AH, Posner MP, Fisher RA. Substitution of tenofovir/emtricitabine for Hepatitis B immune globulin prevents recurrence of Hepatitis B after liver transplantation. *Liver Int* 2012; **32**: 1138-1145 [PMID: 22348467 DOI: 10.1111/j.1478-3231.2012.02770.x]

135 **Teperman LW**, Poordad F, Bzowej N, Martin P, Pungpapong S, Schiano T, Flaherty J, Dinh P, Rossi S, Subramanian GM, Spivey J. Randomized trial of emtricitabine/tenofovir disoproxil fumarate after hepatitis B immunoglobulin withdrawal after liver transplantation. *Liver Transpl* 2013; **19**: 594-601 [PMID: 23447407 DOI: 10.1002/lt.23628]

136 **Gane EJ**, Patterson S, Strasser SI, McCaughan GW, Angus PW. Combination of lamivudine and adefovir without hepatitis B immune globulin is safe and effective prophylaxis against hepatitis B virus recurrence in hepatitis B surface antigen-positive liver transplant candidates. *Liver Transpl* 2013; **19**: 268-274 [PMID: 23447403 DOI: 10.1002/lt.23600]

137 **McGonigal KH**, Bajjoka IE, Abouljoud MS. Tenofovir-emtricitabine therapy for the prevention of hepatitis B recurrence in four patients after liver transplantation. *Pharmacotherapy* 2013; **33**: e170-e176 [PMID: 23744810 DOI: 10.1002/phar.1306]

138 **Angus PW**, Patterson SJ, Strasser SI, McCaughan GW, Gane E. A randomized study of adefovir dipivoxil in place of HBIG in combination with lamivudine as post-liver transplantation hepatitis B prophylaxis. *Hepatology* 2008; **48**: 1460-1466 [PMID: 18925641 DOI: 10.1002/hep.22524]

139 **Cholongitas E**, Papatheodoridis GV, Burroughs AK. Liver grafts

from anti-hepatitis B core positive donors: a systematic review. *J Hepatol* 2010; **52**: 272-279 [PMID: 20034693 DOI: 10.1016/j.jhep.2009.11.009]

140   **Cholongitas E**, Papatheodoridis GV. Review of the pharmacological management of hepatitis B viral infection before and after liver transplantation. *World J Gastroenterol* 2013; **19**: 9189-9197 [PMID: 24409047 DOI: 10.3748/wjg.v19.i48.9189]

141   **Tahara H**, Tanaka Y, Ishiyama K, Ide K, Shishida M, Irei T, Ushitora Y, Ohira M, Banshodani M, Tashiro H, Itamoto T, Asahara T, Imamura M, Takahashi S, Chayama K, Ohdan H. Successful hepatitis B vaccination in liver transplant recipients with donor-specific hyporesponsiveness. *Transpl Int* 2009; **22**: 805-813 [PMID: 19490542 DOI: 10.1111/j.1432-2277.2009.00864.x]

142   **Prieto M**, Gómez MD, Berenguer M, Córdoba J, Rayón JM, Pastor M, García-Herola A, Nicolás D, Carrasco D, Orbis JF, Mir J, Berenguer J. De novo hepatitis B after liver transplantation from hepatitis B core antibody-positive donors in an area with high prevalence of anti-HBc positivity in the donor population. *Liver Transpl* 2001; **7**: 51-58 [PMID: 11150423 DOI: 10.1053/jlts.2001.20786]

143   **Manzarbeitia C**, Reich DJ, Ortiz JA, Rothstein KD, Araya VR, Munoz SJ. Safe use of livers from donors with positive hepatitis B core antibody. *Liver Transpl* 2002; **8**: 556-561 [PMID: 12037788 DOI: 10.1053/jlts.2002.33451]

144   **Chen YS**, Wang CC, de Villa VH, Wang SH, Cheng YF, Huang TL, Jawan B, Chiu KW, Chen CL. Prevention of de novo hepatitis B virus infection in living donor liver transplantation using hepatitis B core antibody positive donors. *Clin Transplant* 2002; **16**: 405-409 [PMID: 12437618]

145   **Nery JR**, Nery-Avila C, Reddy KR, Cirocco R, Weppler D, Levi DM, Nishida S, Madariaga J, Kato T, Ruiz P, Schiff E, Tzakis AG. Use of liver grafts from donors positive for antihepatitis B-core antibody (anti-HBc) in the era of prophylaxis with hepatitis-B immunoglobulin and lamivudine. *Transplantation* 2003; **75**: 1179-1186 [PMID: 12717200 DOI: 10.1097/01.TP.0000065283.98275.FE]

146   **Celebi Kobak A**, Karasu Z, Kilic M, Ozacar T, Tekin F, Gunsar F, Ersoz G, Yuzer Y, Tokat Y. Living donor liver transplantation from hepatitis B core antibody positive donors. *Transplant Proc* 2007; **39**: 1488-1490 [PMID: 17580169 DOI: 10.1016/j.transproceed.2006.11.015]

147   **De Feo TM**, Poli F, Mozzi F, Moretti MP, Scalamogna M; Collaborative Kidney, Liver and Heart North Italy Transplant Program Study Groups. Risk of transmission of hepatitis B virus from anti-HBC positive cadaveric organ donors: a collaborative study. *Transplant Proc* 2005; **37**: 1238-1239 [PMID: 15848681 DOI: 10.1016/j.transproceed.2004.12.041]

148   **Suehiro T**, Shimada M, Kishikawa K, Shimura T, Soejima Y, Yoshizumi T, Hashimoto K, Mochida Y, Maehara Y, Kuwano H. Prevention of hepatitis B virus infection from hepatitis B core antibody-positive donor graft using hepatitis B immune globulin and lamivudine in living donor liver transplantation. *Liver Int* 2005; **25**: 1169-1174 [PMID: 16343068 DOI: 10.1111/j.1478-3231.2005.01165.x]

149   **Dodson SF**, Issa S, Araya V, Gayowski T, Pinna A, Eghtesad B, Iwatsuki S, Montalvo E, Rakela J, Fung JJ. Infectivity of hepatic allografts with antibodies to hepatitis B virus. *Transplantation* 1997; **64**: 1582-1584 [PMID: 9415560]

150   **Takemura N**, Sugawara Y, Tamura S, Makuuchi M. Liver transplantation using hepatitis B core antibody-positive grafts: review and university of Tokyo experience. *Dig Dis Sci* 2007; **52**: 2472-2477 [PMID: 17805972 DOI: 10.1007/s10620-006-9656-5]

151   **Bárcena Marugán R**, García-Hoz F, Vázquez Romero M, Nash R, Mateos M, González Alonso R, García González M, García Plaza A. Prevention of de novo hepatitis B infection in liver allograft recipients with previous hepatitis B infection or hepatitis B vaccination. *Am J Gastroenterol* 2002; **97**: 2398-2401 [PMID: 12358263 DOI: 10.1111/j.1572-0241.2002.05994.x]

152   **Fox AN**, Terrault NA. The option of HBIG-free prophylaxis against recurrent HBV. *J Hepatol* 2012; **56**: 1189-1197 [PMID: 22274310 DOI: 10.1016/j.jhep.2011.08.026]

153   **Ishigami M**, Ogura Y, Hirooka Y, Goto H. Change of strategies and future perspectives against hepatitis B virus recurrence after liver transplantation. *World J Gastroenterol* 2015; **21**: 10290-10298 [PMID: 26420956 DOI: 10.3748/wjg.v21.i36.10290]

154   **Roche B**, Roque-Afonso AM, Nevens F, Samuel D. Rational Basis for Optimizing Short and Long-term Hepatitis B Virus Prophylaxis Post Liver Transplantation: Role of Hepatitis B Immune Globulin. *Transplantation* 2015; **99**: 1321-1334 [PMID: 26038873 DOI: 10.1097/TP.0000000000000777]

155   **Hu TH**, Chen CL, Lin CC, Wang CC, Chiu KW, Yong CC, Liu YW, Eng HL. Section 14. Combination of entecavir plus low-dose on-demand hepatitis B immunoglobulin is effective with very low hepatitis B recurrence after liver transplantation. *Transplantation* 2014; **97** Suppl 8: S53-S59 [PMID: 24849836 DOI: 10.1097/01.tp.0000446278.43804.f9]

156   **Gish RG**, Given BD, Lai CL, Locarnini SA, Lau JY, Lewis DL, Schluep T. Chronic hepatitis B: Virology, natural history, current management and a glimpse at future opportunities. *Antiviral Res* 2015; **121**: 47-58 [PMID: 26092643 DOI: 10.1016/j.antiviral.2015.06.008]

157   **Wadhawan M**, Gupta S, Goyal N, Taneja S, Kumar A. Living related liver transplantation for hepatitis B-related liver disease without hepatitis B immune globulin prophylaxis. *Liver Transpl* 2013; **19**: 1030-1035 [PMID: 23788470 DOI: 10.1002/lt.23692]

158   **Fung J**, Chan SC, Cheung C, Yuen MF, Chok KS, Sharr W, Chan AC, Cheung TT, Seto WK, Fan ST, Lai CL, Lo CM. Oral nucleoside/nucleotide analogs without hepatitis B immune globulin after liver transplantation for hepatitis B. *Am J Gastroenterol* 2013; **108**: 942-948 [PMID: 23629601 DOI: 10.1038/ajg.2013.111]

159   **Fung J**, Cheung C, Chan SC, Yuen MF, Chok KS, Sharr W, Dai WC, Chan AC, Cheung TT, Tsang S, Lam B, Lai CL, Lo CM. Entecavir monotherapy is effective in suppressing hepatitis B virus after liver transplantation. *Gastroenterology* 2011; **141**: 1212-1219 [PMID: 21762659 DOI: 10.1053/j.gastro.2011.06.083]

160   **Fung J**, Lo R, Chan SC, Chok K, Wong T, Sharr W, Cheung TT, Chan AC, Dai WC, Sin SL, Ng I, Lai CL, Yuen MF, Lo CM. Outcomes including liver histology after liver transplantation for chronic hepatitis B using oral antiviral therapy alone. *Liver Transpl* 2015; **21**: 1504-1510 [PMID: 26194746 DOI: 10.1002/lt.24218]

161   **Fung J**, Wong T, Chok K, Chan A, Cheung TT, Dai JW, Sin SL, Ma KW, Ng K, Ng KT, Seto WK, Lai CL, Yuen MF, Lo CM. Long-term outcomes of entecavir monotherapy for chronic hepatitis B after liver transplantation: Results up to 8 years. *Hepatology* 2017; **66**: 1036-1044 [PMID: 28370215 DOI: 10.1002/hep.29191]

162   **Zheng JN**, Zou TT, Zou H, Zhu GQ, Ruan LY, Cheng Z, Van Poucke S, Zheng MH. Comparative efficacy of oral nucleotide analogues for the prophylaxis of hepatitis B virus recurrence after liver transplantation: a network meta-analysis. *Expert Rev Anti Infect Ther* 2016; **14**: 979-987 [PMID: 27491868 DOI: 10.1080/14787210.2016.1220831]

163   **Fung J**, Wong T, Chok K, Chan A, Sin SL, Cheung TT, Dai WC, Ng K, Ng K, Man K, Seto WK, Lai CL, Yuen MF, Lo CM. Oral Nucleos(t)ide Analogs Alone After Liver Transplantation in Chronic Hepatitis B With Preexisting rt204 Mutation. *Transplantation* 2017; **101**: 2391-2398 [PMID: 28731907 DOI: 10.1097/tp.0000000000001883]

164   **Couto CA**, Bittencourt PL, Farias AQ, Lallee MP, Cançado EL, Massarollo PC, Mies S. Human polyclonal anti-hepatitis B surface antigen immunoglobulin reduces the frequency of acute rejection after liver transplantation for chronic hepatitis B. *Rev Inst Med Trop Sao Paulo* 2001; **43**: 335-337 [PMID: 11781604]

165   **Wong SY**, Levitsky J. Chronic rejection related to hepatitis B immunoglobulin discontinuation in a liver transplant recipient. *Transpl Int* 2011; **24**: e104-e106 [PMID: 21902731 DOI: 10.1111/j.1432-2277.2011.01334.x]

166   **Lee EC**, Kim SH, Lee SD, Park H, Lee SA, Park SJ. High-dose hepatitis B immunoglobulin therapy in hepatocellular carcinoma with hepatitis B virus-DNA/hepatitis B e antigen-positive patients after living donor liver transplantation. *World J Gastroenterol*

2016; **22**: 3803-3812 [PMID: 27076765 DOI: 10.3748/wjg.v22. i14.3803]

167 **Lenci I**, Tisone G, Di Paolo D, Marcuccilli F, Tariciotti L, Ciotti M, Svicher V, Perno CF, Angelico M. Safety of complete and sustained prophylaxis withdrawal in patients liver-transplanted for HBV-related cirrhosis at low risk of HBV recurrence. *J Hepatol* 2011; **55**: 587-593 [PMID: 21251938 DOI: 10.1016/j.jhep.2010.12.036]

168 **Lenci I**, Baiocchi L, Tariciotti L, Di Paolo D, Milana M, Santopaolo F, Manzia TM, Toti L, Svicher V, Tisone G, Perno CF, Angelico M. Complete hepatitis B virus prophylaxis withdrawal in hepatitis B surface antigen-positive liver transplant recipients after longterm minimal immunosuppression. *Liver Transpl* 2016; **22**: 1205-1213 [PMID: 27272189 DOI: 10.1002/lt.24493]

169 **Roche B**, Feray C, Gigou M, Roque-Afonso AM, Arulnaden JL, Delvart V, Dussaix E, Guettier C, Bismuth H, Samuel D. HBV DNA persistence 10 years after liver transplantation despite successful anti-HBS passive immunoprophylaxis. *Hepatology* 2003; **38**: 86-95 [PMID: 12829990 DOI: 10.1053/jhep.2003.50294]

170 **Kasraianfard A**, Watt KD, Lindberg L, Alexopoulos S, Rezaei N. HBIG Remains Significant in the Era of New Potent Nucleoside Analogues for Prophylaxis Against Hepatitis B Recurrence After Liver Transplantation. *Int Rev Immunol* 2016; **35**: 312-324 [PMID: 24911598 DOI: 10.3109/08830185.2014.921160]

171 **Wang SH**, Loh PY, Lin TL, Lin LM, Li WF, Lin YH, Lin CC, Chen CL. Active immunization for prevention of De novo hepatitis B virus infection after adult living donor liver transplantation with a hepatitis B core antigen-positive graft. *Liver Transpl* 2017; **23**: 1266-1272 [PMID: 28691231 DOI: 10.1002/lt.24814]

172 **Cai D**, Mills C, Yu W, Yan R, Aldrich CE, Saputelli JR, Mason WS, Xu X, Guo JT, Block TM, Cuconati A, Guo H. Identification of disubstituted sulfonamide compounds as specific inhibitors of hepatitis B virus covalently closed circular DNA formation. *Antimicrob Agents Chemother* 2012; **56**: 4277-4288 [PMID: 22644022 DOI: 10.1128/aac.00473-12]

173 **Petersen J**, Dandri M, Mier W, Lütgehetmann M, Volz T, von Weizsäcker F, Haberkorn U, Fischer L, Pollok JM, Erbes B, Seitz S, Urban S. Prevention of hepatitis B virus infection in vivo by entry inhibitors derived from the large envelope protein. *Nat Biotechnol* 2008; **26**: 335-341 [PMID: 18297057 DOI: 10.1038/nbt1389]

174 **Volz T**, Allweiss L, Ben MBarek M, Warlich M, Lohse AW, Pollok JM, Alexandrov A, Urban S, Petersen J, Lütgehetmann M, Dandri M. The entry inhibitor Myrcludex-B efficiently blocks intrahepatic virus spreading in humanized mice previously infected with hepatitis B virus. *J Hepatol* 2013; **58**: 861-867 [PMID: 23246506 DOI: 10.1016/j.jhep.2012.12.008]

175 **Girlanda R**, Mohsen AH, Smith H, Sablon E, Yuen MF, O'Grady J, Muiesan P, Rela M, Heaton N, Norris S. Hepatitis B virus genotype A and D and clinical outcomes of liver transplantation for HBV-related disease. *Liver Transpl* 2004; **10**: 58-64 [PMID: 14755779 DOI: 10.1002/lt.20004]

176 **Gaglio P**, Singh S, Degertekin B, Ishitani M, Hussain M, Perrillo R, Lok AS; National Institutes of Health Hepatitis B Virus-Orthotopic Liver Transplantation Study Group. Impact of the hepatitis B virus genotype on pre- and post-liver transplantation outcomes. *Liver Transpl* 2008; **14**: 1420-1427 [PMID: 18825703 DOI: 10.1002/lt.21563]

177 **Lo CM**, Cheung CK, Lau GK, Yuen MF, Liu CL, Chan SC, Fan ST, Wong J. Significance of hepatitis B virus genotype in liver transplantation for chronic hepatitis B. *Am J Transplant* 2005; **5**: 1893-1900 [PMID: 15996236 DOI: 10.1111/j.1600-6143.2005.00952.x]

Baishideng®

Published by **Baishideng Publishing Group Inc**
7901 Stoneridge Drive, Suite 501, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.f6publishing.com/helpdesk
http://www.wjgnet.com