

MANAGEMENT OF HEPATITIS B VIRUS INFECTION IN LIVER TRANSPLANT RECIPIENTS

Joy Varghese,¹ Jayanthi Venkataraman,¹ Mettu Srinivas Reddy,¹
Mohamed Rela^{1,2}

1. Institute of Liver Diseases & Transplantation, Global Hospitals & Health City, Chennai, India
2. Kings College Hospital, London, United Kingdom

Disclosure: No potential conflict of interest.

Citation: EMJ Hepatol. 2013;1:58-67.

ABSTRACT

Hepatitis B virus (HBV)-related liver disease is a common indication for liver transplantation (LT) in Asian countries.¹ When left untreated, the overall five-year survival rate in HBV-related cirrhosis is 71%, which in cases of decompensated cirrhosis decreases to 14%.² In the 1980s, hepatitis B-related acute liver failure and chronic liver disease (CLD) were considered contraindications for LT because of almost universal graft reinfection and high rates of graft and recipient failure (>50%).³⁻⁴ These patients had severe and rapidly progressive liver disease with a two-year graft and patient survival of 50% compared to 80% in those transplanted for non-HBV-related CLD.⁵ As a result, there were fewer LT for HBV liver disease for several years.⁶ However, with the introduction of nucleoside and nucleotide analogues and the use of intra and post-operative hepatitis B immunoglobulin (HBIG), there was renewed interest in the application of LT in these patients. There was a significant decrease in post-operative HBV recurrence rates.⁷⁻⁹ The current overall survival of patients transplanted for HBV-related cirrhosis has improved to 85% at one year, and 75% at five years.^{7,10-12} The present review highlights issues pertaining to HBV reinfection and *de novo* infection in LT recipients with recommendations for its management.

Keywords: Hepatitis B virus (HBV), liver transplantation, cirrhosis, nucleoside, nucleotide.

A. HBV REINFECTION

Reinfection after liver transplant can be either early or delayed.

Early post-operative HBV reinfection in allograft:

This is determined by HBV DNA levels in the pre-operative period. A high pre-LT HBV DNA level predisposes to high rates of early reinfection as compared to those with low or undetectable levels of HBV DNA. Marzona et al.,¹³ in a study of 177 LT recipients receiving HBIG with or without lamivudine, noted HBV recurrence of 50%, 7.5%, and 0% when serum HBV DNA levels at the time of transplant were 100,000, 200-100,000, and less than 200 copies/mL respectively. The authors concluded that serum HBV DNA greater than 5 log₁₀ copies/mL (>10⁵ copies/mL) at the time of transplant was associated with significantly higher risk of early HBV recurrence.

Delayed reinfection: Despite adequate pre-transplant antiviral therapy to suppress/eradicate HBV, a few potential reservoirs of the virus remain in the carriers. These include peripheral blood mononuclear cells (PBMC), bone marrow, spleen, gonads, thyroid gland, kidneys, pancreas and adrenal glands,⁷ where the antivirals fail to achieve optimal drug levels. The introduction of steroids as part of immunosuppression in the post-transplant period reactivates the hitherto dormant virus, with steroids known to enhance HBV DNA gene expression (glucocorticoid-responsive transcriptional gene enhancer).¹⁴ In the absence of immune-prophylaxis, the risk of reinfection with HBV is 33% to 78%.¹⁵⁻¹⁹

Factors predicting post-liver transplant reinfection

Pre-transplant factors

High risk factors:

i. Resistance/mutation to oral antiviral drugs: Nucleoside/nucleotide agents are given before LT with an intention to reduce replication and reduce the risk of HBV recurrence after LT. Lamivudine resistance shares resistance patterns with other oral antiviral drugs such as telbivudine as well as entecavir.

ii. HBV DNA mutation: Mutation in the HBV surface (S) and polymerase (P) gene before LT is associated with higher post-LT HBV recurrence.²⁰⁻²²

iii. LT recipients who have anti-HBc positive and HBsAg negative before LT: There are reports of reactivation of HBV virus if the recipient is anti-HBcore antibody positive, despite receiving non-HBsAg and anti-HBc negative liver graft. The virus in these patients is in the dormant state within non-liver sites, and in the presence of immunosuppressants, gets reactivated after transplant. In a study by Abdelmalek et al.,²³ of the 22 patients on the waiting list for LT who were HBsAg negative and anti-HBc positive patients, HBV DNA was detected in the liver in 5 (23%) before transplant, which persisted in 2 in the explanted liver.²³ However, none of the recipients became HBsAg positive, nor did they develop clinical hepatitis after transplant.

iv. Reinfection in the immune-compromised recipients: Associated HIV infection and an immune-compromised state significantly increases HBV recurrence in the post-operative period.^{14,24}

v. Transmission via contaminated blood products or healthcare personnel in the peri-operative period: It is not uncommon if the blood products contain occult HBV infection (i.e: HBsAg negative, Total HBcore antibody positive with detectable HBV DNA level).

Low risk factors:

i. Fulminant hepatitis B: HBV reinfection rate in LT recipients following fulminant hepatic failure (FHF) is low.⁹ As HBV-related hepatocyte injury is an immune mediated mechanism rather than due to direct viral pathogenicity, viral load in FHF is usually lesser than in HBV-related cirrhosis. In a study by Roche et al.,¹² no reinfection was seen in 8 patients who had LT for FHF during a follow up of ten years.

ii. Coinfection with Hepatitis Delta virus (HDV): Recurrence rates of HBV are low when there is superinfection with HDV, while HDV competitively inhibits the fixing of the HBV to hepatocytes. Roche et al.¹² noted that the ten-year actuarial risk of HBsAg

recurrence in HBV and HDV-related cirrhosis was 15.3%, in comparison to 56.5% in non-Delta Hepatitis B-related cirrhosis.

Intraoperative factors

The use of parenteral corticosteroids in an anhepatic phase can induce resurgence of HBV secondary to the stimulatory effect of steroid therapy on the glucocorticoid-responsive enhancer region of the HBV genome.²⁴⁻²⁵

Post-transplant factors

i. Use of immunosuppressive drugs. (particularly steroid).

ii. Low anti HBs antibody level (i.e: Less than 100IU/mL): Despite the use of HBIG, the antibody to HBsAg may not be optimal, either due to poor compliance or failure of the immunoprophylaxis, resulting in recurrence of infection.

iii. Combination of HBIG and oral antiviral agents.

iv. Recipient's compliance.

B. DE NOVO HBV INFECTION

De novo post-transplant HBV infection is defined as the appearance of HBsAg in a transplant recipient not previously known to have a HBV infection. The clinical course in these transplant recipients is often relatively mild in comparison to recurrent HBV infections in the transplant population.²⁶⁻²⁸ This may present itself as an asymptomatic elevation in serum transaminase levels.

The possible potential modes of acquiring a *de novo* infection are:

Emergence of occult HBV infection: This is of particular concern in regions with high endemicity of HBV infection and a high prevalence of anti-HBc positivity.¹⁵ The source of occult infection may be the donor or the recipient himself.²⁹

i. HBsAg positive or anti-HBc positive donor to a HBV negative recipient: Approximately, 10% of recipients would acquire *de novo* HBV infection, when a critically ill HBsAg negative end stage liver disease (ESLD) patient receives a liver allograft from a HBsAg positive donor^{15,30} or a donor who is anti-HBc positive (total).^{15,26,28-29,31-34} This may be related to a high viral load within the liver.³² Dickson et al.³¹ reported conversion to HBsAg positivity in 18 recipients (78%) when donors were anti-HBc positive as compared to

3 of 651 (0.5%) recipients when donors were anti-HBc negative.³⁵ The donor-transmitted *de novo* HBV infection was mild in most cases; 50% of patients had normal serum aminotransferases, while 85% had no or only mild inflammatory activity on post-LT liver biopsy at the end of one year. However, there was a decrease in the four-year survival rate (featuring an adjusted mortality hazard ratio of 2.4; 95% confidence interval, 1.4-4.0).

ii. Anti-HBs positive recipient: The recipient is not free from acquiring a *de novo* HBV infection, especially when the donor is anti-HBc positive.^{29,36-37} The donor is likely to have an occult HBV infection (undetectable HBV DNA in the sera or extra hepatic tissue), which makes its appearance in presence of immunosuppressive therapy.

iii. Anti-HBc positive recipient: Even in the absence of serologic evidence of viral replication, HBV-DNA may be detectable in the livers of anti-HBc positive recipients.³⁸ Oral antiviral drugs should be continued in all anti-HBc negative recipients if receiving from an anti-HBc positive donor.

C. STRATEGIES TO PREVENT HBV REINFECTION

The natural history of HBV reinfection in post-LT has shown that not all patients get HBV infections. A small group of recipients even without post-LT HBV prophylaxis have survived without recurrence.⁴

In recent times, with the introduction of newer antiviral analogues for treatment of HBV positive patients with detectable serum HBV DNA, the post-operative recurrence rates are likely to be less than 10%. Hepatitis B vaccination to all non-HBV related liver cirrhosis will prevent occult HBV-related *de novo* infection.

Management of HBV positive patients during and after LT

During LT

In the anhepatic phase, a high dose of 10,000IU of HBIG is given intravenously. Nowadays, a low intramuscular dose (2,000IU) of HBIG has been proven to be as effective as a high dose of HBIG.³⁹⁻⁴¹

After LT

The aims of treatment in the post-LT setting are to minimise the risk of HBV infection of the graft and to decrease the incidence of significant HBV-related

liver disease over the long-term. The main agents available for the clinician are:

- Oral antiviral agents (Nucleoside/tide analogues).
- HBIG-nucleoside/tide combination therapy.

Combination therapy with HBIG and oral antiviral drugs are the current gold standard for post-LT HBV therapy. Recent studies have shown that newer oral antiviral drugs such as entecavir/tenofovir as monotherapy are as effective as combination therapy.⁴²⁻⁴³

i. Nucleoside/tide analogues

Nucleoside/nucleotide analogues as a single agent have been used as prophylaxis against HBV infection in post-LT recipients. In this case, oral antivirals are introduced in the pre transplant period and continued indefinitely post-operatively. As it is a HBV DNA reverse transcriptase inhibitor, it inhibits viral DNA synthesis.

Lamivudine monotherapy: A multicentre study by the Lamivudine North American Transplant Group, which enrolled 77 HBsAg positive (60% of them had detectable HBV DNA as well as HBeAg positive) subjects on transplant waiting lists, lamivudine as single therapy showed favourable results. 42 subjects underwent LT; 60% were HBsAg negative for more than 12 weeks after LT. However, a major drawback with lamivudine has been the emergence of a resistant hepatitis B virus (YMDD) mutant^{39,44} even prior to transplant, causing problems in management of recipients in the post-transplant period.⁴⁵

The incidence of post-transplant resistance ranges from 10% to 45% within one year of treatment^{46,47} and almost 50% in six years. In the number of *de novo* HBV infections in 110 patients (i.e from livers of donors who were HBsAg negative and anti-HBc positive) given lamivudine prophylaxis, the rate of *de novo* infection was 3.6% after a mean follow-up of 25 months.²⁶ Hence, the drug is not considered the first-line of management in LT.

Adefovir has both *in vitro* and *in vivo*⁴⁸ efficacy against both wild-type and lamivudine-resistant HBV. Perillo and colleagues⁴⁹ enrolled 128 pre-LT and 196 post-LT patients all of whom had detectable HBV DNA despite ongoing lamivudine therapy. Median lamivudine exposure at the time of enrolment was 69 weeks in the pre-LT group (128 patients) and 56 weeks in the post-LT group (196 patients).

Adefovir (10mg/day or 5mg/day in presence of renal dysfunction) was added to the treatment schedule of lamivudine with/without HBIG therapy. Among subjects completing 48 weeks of adefovir therapy, the median HBV-DNA had decreased by 3.4 log copies/mL in the pre-LT group and 3.3 log copies/mL in the post-LT group. Majority of patients in both treatment groups experienced stabilisation or improvement in Child-Pugh scores. Survival following one year of adefovir therapy was 84% in the pre-LT group and 93% in the post-LT group. Extended data from this ongoing study demonstrated continued efficacy up to 144 weeks of therapy.⁵⁰

A major drawback with adefovir is its nephrotoxicity. The concomitant use of nephrotoxic medications (i.e. calcineurin inhibitors) in post-LT patients or those with prior history of renal injury has limited its use among the transplant population. In the aforementioned study, adefovir had to be stopped in 2% of subjects in the post-LT group due to nephrotoxicity.⁴⁹ Adefovir resistance has been described in a post-LT patient with recurrence of HBV infection.⁴⁸

Entecavir⁵¹⁻⁵³ is associated with lower rates of drug resistance, and is the recommended drug for life-long treatment. Its dual action against wild-type and lamivudine-resistant HBV, and its favourable toxicity profile, offers promise for its potential effectiveness in the post-LT population. The pilot study of Tenofovir post-LT shows that it is safe and efficacious.⁴³

To summarise, entecavir is recommended as a first-line antiviral agent in nucleoside naïve transplant patients because of its greater potency, low rates of drug resistance, and nephrotoxicity.

ii. Hepatitis B immune globulin (HBIG)

This was first administered as passive immunoprophylaxis to a HBsAg positive LT recipient in 1978.⁵⁴ Samuel et al.⁵⁵ carried out a retrospective analysis of patients transplanted for HBV in 17 European centres to determine the role of HBIG immune-prophylaxis in HBsAg positive transplant recipients. HBIG is a polyclonal preparation of human anti-HBs purified from pooled donor plasma. It is given intravenously as a 10,000IU bolus dose during the anhepatic phase, followed by daily doses of 2,000IU during the first week. Subsequent doses are either given monthly or in accordance with anti-HBs titres. A trough anti-HBs titre of at least 150IU/L is considered as protective. Several subsequent studies have further shown a reduction

in reinfection, and improved patient and graft survival HBIG prophylaxis.^{4,56-57} Early reinfection can be prevented by administration of HBIG in the intraoperative anhepatic phase and in the immediate post-operative period to maintain anti-HBs levels of more than 100-150IU/mL. Late reinfection can be prevented by continuing HBIG for a longer period of time in combination with antiviral medications. Overall, immunoprophylaxis strategy significantly reduces the actuarial ten-year risk recurrence rate to 25.4% and the ten-year survival rate increased to 74%.¹²

There are marked differences in the dose and duration of HBIG across various transplant centres. The serum HBV DNA level at the time of transplant is an important predictor of HBV reinfection.

The mechanism of action of HBIG is unclear, but it is likely that it binds to HBV receptors on uninfected hepatocytes, and occupies potential viral entry sites. It undergoes endocytosis after binding to the hepatocyte receptor site and decreases the release of HBsAg from the cell.⁵⁸ The hepatocytes are subsequently protected from infection by HBV particles which are released from extrahepatic reservoirs⁵⁹ following immunosuppression in the post-transplant period. In circulation, HBIG also has a direct binding and neutralising effect on circulating virions. HBIG also induces antibody-dependent cell-mediated cytotoxicity.

iii. HBIG and nucleoside/nucleotide combination therapy

HBIG immunoprophylaxis has been less successful in preventing reinfection in HBeAg positive patient or those with significant detectable HBV DNA viral load i.e. >100,000 copies/mL (10^5).^{4,13,60} Antiviral therapy with nucleoside/nucleotide analogues before transplant decreases the risk of reinfection by decreasing the amount of circulating virus at the time of transplant and prolonging the half-life of HBIG.⁶¹

Combination therapy of HBIG and nucleoside analogues reduces recurrence rates to less than 10%. The earliest published data, in this regard, was a 1998 study enrolling 14 HBsAg positive LT candidates.⁴⁴ Lamivudine was initiated pre-LT in 10 subjects, 4 of whom had detectable HBV DNA. HBIG therapy was initiated during the anhepatic phase of transplant, and all patients received combination HBIG and lamivudine therapy after LT. After a median follow-up of 387 days (range, 49-525) post-transplant,

	Hepatitis B Immunoglobulin	Nucleoside/Nucleotide Analogs
Mode of action	HBV DNA reverse transcriptase inhibitor, hence inhibits viral DNA synthesis	Unclear; it has direct binding and neutralising effect on circulating virions
Duration of therapy	Life-long	Life-long
Resistance	Vaccine escape mutant	Drug resistance (more with lamivudine; less with entecavir/tenofovir)
Cost	Costly	Cheaper

Table 1. HBIG versus oral anti-viral drugs

HBsAg and HBV-DNA remained undetectable in 13 surviving subjects.

The efficacy of lamivudine/HBIG combination therapy in the prevention of HBV recurrence has been confirmed in subsequent series, including several protocols with low-dose HBIG,^{20,40,62-64} with the combination also shown to be cost-effective.

A meta-analysis of two prospective and four retrospective studies where HBIG alone was compared with HBIG plus lamivudine concluded that combination therapy was associated with a significantly lower rate of HBV-related deaths and all-cause mortality.⁶⁵⁻⁶⁶ The recurrence rate was also low in a select population.^{66,67} Contradictory to this study, in a systematic review which included patients who received a liver from donors who were HBsAg negative and anti-HBc positive, the rate of *de novo* HBV infection in 73 patients who received HBIG and lamivudine prophylaxis was 2.7% after a mean follow-up of 31 months.⁶⁸ This was similar to that seen for lamivudine monotherapy (3.6%), suggesting that the addition of HBIG to the regimen did not provide any added benefit.

Combination of lamivudine plus adefovir in certain select population also prevents HBV recurrence.^{69,70} In one study, 34 adults on HBIG and lamivudine prophylaxis followed up for at least 12 months after transplant showed no recurrent HBV in the graft.⁷¹ In this study, at the end of 12 months, patients were divided into two groups, one group receiving adefovir (10mg) along with lamivudine and the other lamivudine in combination with HBIG. One patient in the adefovir group became transiently positive for HBsAg, one other had deterioration of renal function requiring dose adjustment and then cessation of

adefovir after 15 months. The rest of the patients in this group had undetectable HBsAg and HBV DNA during a median follow-up of 21 months. The authors estimated that the adefovir plus lamivudine group was similarly effective and substantially less costly than the lamivudine plus HBIG approach (\$8,290 versus \$13,718 per treatment year).

The study concluded that antiviral therapy alone without HBIG was as effective in preventing HBV reinfection in a select group of patients. However, most patients in the study were at a relatively low risk; only 7 of 30 had pre-transplant detectable HBV DNA. Furthermore, HBIG was stopped after the most vulnerable period (the first 12 months). The results of the study cannot be generalised to high-risk patients i.e. those with initially high HBV DNA levels or patients in the first year after transplantation.

More recently, HBIG was substituted with tenofovir and emtricitabine combination to prevent recurrence of HBV infection.⁷² The study showed prevention of HBV DNA recurrence in 100% (20/20) of patients who were compliant with the medication, and led to substantial cost savings over HBIG-containing regimens.

Issues pertaining to HBIG

HBIG is expensive. Long-term HBIG prophylaxis post-LT can significantly increase the cost of post-transplant care. Several studies have been undertaken to find alternative regimens that minimise the use of HBIG without sacrificing the benefit of low HBV recurrence. Fox et al.⁷³ has extensively reviewed the literature and has highlighted HBIG-free therapeutic options.

(iv) Alternatives to standard HBIG dose

This includes modification in method, frequency and duration of HBIG administration.

Modification in the method of HBIG administration (Use of low-dose intramuscular (IM) HBIG administration): Intramuscular administration of HBIG has been reported to be as effective as IV administration and also cheaper than IV administration. Several protocols have investigated the use of intramuscular HBIG either alone³⁹ or as an addition to an antiviral agent.⁴⁰ The Sawyer et al.⁴¹ study included 147 patients who received low-dose HBIG intramuscularly (400-800IU daily for one week followed by monthly doses) plus lamivudine (100mg daily) following LT.⁴¹ Before transplantation, patients with detectable HBV DNA received lamivudine (100 mg PO daily). Patient survival was 92% at one year and 88% at five years. The actuarial risk of HBV recurrence was only 1% at one year and 4% at five years. More than 50% of patients in this study had undetectable HBV DNA at the time of transplant, potentially contributing to the favourable results. Thus, low-dose HBIG can be recommended in combination with a nucleoside/nucleotide agent when HBV DNA viral load is low or undetectable in the pre-transplant period.

Modification in frequency of HBIG administration (On-demand administration of HBIG based on measurement of serum anti-HBs titres): McGory and colleagues⁵⁶ reported low rates of disease recurrence in HBsAg positive subjects undergoing LT following on-demand HBIG administration aimed at maintaining serum anti-HBs titres >500IU/L. 17 of 27 subjects (63%) were HBeAg-positive pre-LT, and disease recurrence was observed in only 2 subjects, neither of whom were able to maintain target anti-HBs titres. Low anti-HBs titre of 100-150IU/L has also shown low risk for disease recurrence.⁵⁵

Modification in duration of HBIG administration (Maintenance with oral antiviral drugs): The withdrawal of HBIG after a defined course of combination HBIG and oral antiviral drugs has also been shown to be effective, particularly if combination antiviral therapy is used. Choloangitas et al.⁴² stopped HBIG at least 12 months after LT. 40% of their patients received entecavir or tenofovir monoprophyllaxis. The study confirmed that this protocol provided effective antiviral prophylaxis and only 3 (6.3%) of the 47 patients had HBV recurrence 24 months (range: 6 to 40 months) after HBIG withdrawal.

Newer formulations with longer lasting levels of circulating antibodies include OMRI-Hep-B preparation. This may require less frequent administration with a reduction in cost. The half-life of this preparation is significantly longer than standard therapy (22 versus 13 days).⁷⁴ Further studies are needed to confirm these results.

Combined passive immunoprophylaxis with active immunisation: HBV vaccination after HBIG therapy has been tried to prevent HBV reinfection in post-LT, but the results are conflicting.⁶⁰⁻⁶¹ The anti-HBs titres achieved in the responders were low despite the use of higher doses and multiple courses of vaccine.^{21,75-76}

Sanchez-Fueyo et al.⁶¹ selected 17 HBsAg positive LT recipients, 11 of whom had undergone LT for CLD and 6 for FHF. All subjects were HBV-DNA negative and HBeAg negative before LT, and all received HBIG for at least 18 months post-LT without evidence of HBV recurrence. HBV vaccination began several weeks after the final HBIG dose. 14 of 17 subjects (82%) responded to vaccination (6 after 3 vaccine doses, and 8 more after 3 additional vaccine doses) with detectable anti-HBs titres above a predefined threshold; there was no reported evidence of HBV recurrence for as long as 102 months of follow-up. More recent studies using new vaccines and adjuvants have been more encouraging but further studies are necessary to confirm the results.⁷⁷⁻⁷⁸

Use of hyperimmune plasma (HIP) transfusion: Fresh frozen plasma obtained from blood donors with high anti-HBs levels (hyperimmune plasma, HIP) containing at least 4,500IU anti-HBs has been used as an alternative treatment for HBV recurrence prophylaxis post-LT. In a study by Bihl et al.,⁷⁹ 21 HBV-related LT recipients received HIP starting at transplantation, followed by long-term combination treatment with nucleoside analogue. During a mean follow-up time of 4.5 years (range 0.5-12.6), each patient received on average 8.2 HIP per year (range 5.8-11.4). Anti-HBs terminal elimination kinetic after HIP administration was 20.6 days (range 13.8-30.9), which is comparable to values reported for commercial HBIG products. All 21 patients remained free of HBV recurrence during follow-up. There was no transfusion-transmitted infection. The cost for one HIP unit was US \$140; the average yearly HBIG treatment cost was significantly low at US \$148 per patient as compared to US \$25,000 to 100,000 for commercial HBIG.

Subcutaneous HBIG injection: A recent study on weekly subcutaneous injections (500IU & 1000IU in

body weight of <75Kg & >75Kg respectively) of HBIG for 48 weeks in 135 HBV-related LT recipient shows that 97.8% of them had an anti-HBs level of more than 150IU/L (median of 232IU/L) with the least side effects⁸⁰ similar to previous studies.⁸¹⁻⁸²

Oral antiviral drugs alone without HBIG: A study on a combination of HBIG with entecavir in the first five weeks after LT, followed by entecavir monotherapy alone for one year, shows 96.6% and 96.4% disease-free survival in one year & two years follow-up respectively.⁸³ The Fung et al.⁵² study on entecavir monotherapy without HBIG, with a median follow-up of 26 months on 80 post-LT recipients, shows HBV DNA to be undetectable in 98.8%, with HBsAg loss in 91% recipients. Similarly, tenofovir without HBIG also shows effective control on HBV recurrence in post-solid organ recipients.^{43,72}

Drawbacks of HBIG

The major drawback with HBIG is its long-term use, the cost, and inconvenience of administration. In India, protocols that use high dose IV HBIG as described above are expensive i.e. Rs360,000 in the first year which includes the cost of IV infusion sets and monitoring. In the USA, the estimated cost is as high as \$120,000 per year per patient.⁸⁴ Yet another problem is the failure to procure a constant supply of HBIG.⁵⁶ Adverse effects of HBIG, though rare, include:

- i. Immune mediated reactions such as back pain, skin rash, and myalgia. Premedication is frequently not necessary.
- ii. Mercury toxicity associated with intravenous administration of HBIG due to a thimerosal vehicle.

iii. Emergence of “a” determinant escape mutations,^{21,85} which fails to get neutralised with HBIG administration. In a retrospective study, the estimated frequency of HBIG failure was 8% due to “a” determinant mutations at 28 months of therapy. Escape HBV mutations have occurred in recipients who have received anti-HBc positive liver grafts,⁸⁶ despite adequate dosing of HBIG.

Thus, at present, a rational approach to the prophylaxis of *de novo* HBV infection post-LT would be based on risk stratification i.e. pre-transplant HBV serology and viremic status which includes detectable anti-HBc, HBsAg or HBV-DNA in the donor and in the transplant recipient.⁸⁷⁻⁸⁸

SUMMARY

Detectable viremia and/or HBeAg positivity at the time of transplant are significant predictors of disease recurrence. Implementation of pre transplant treatment strategies will lower the burden of viral replication in transplant candidates. Newer oral anti-viral therapy, such as entecavir/tenofovir either as monotherapy or with HBIG, shows promising outcomes to prevent HBV reinfection in post-LT period. A safe time threshold for discontinuation of HBIG post-LT is not known, particularly among patients with a high risk for recurrence, i.e. those with detectable viremia at the time of transplant. Vaccination in the future will prevent HBV infection and reduce the disease burden worldwide. Future guidelines will help resolve some of these issues.

REFERENCES

1. Ho BM, So SK, Esquivel CO, Keeffe EB. Liver transplantation in Asian patients with chronic hepatitis B. *Hepatology*. 1997;25(1):223-5.
2. de Jongh FE, Janssen HL, de Man RA, Hop WC, Schalm SW, van Blankenstein M. Survival and prognostic indicators in hepatitis B surface antigen-positive cirrhosis of the liver. *Gastroenterology*. 1992;103(5):1630-5.
3. Todo S, Demetris AJ, Van Thiel D, Teperman L, Fung JJ, Starzl TE. Orthotopic liver transplantation for patients with hepatitis B virus-related liver disease. *Hepatology*. 1991;13(4):619-26.
4. Terrault N, Roche B, Samuel D. Management of the hepatitis B virus in the liver transplantation setting: a European and an American perspective. *Liver Transpl*. 2005;11(7):716-32.
5. Kim WR, Poterucha JJ, Kremers WK, Ishitani MB, Dickson ER. Outcome of liver transplantation for hepatitis B in the United States. *Liver Transpl*. 2004;10(8):968-74.
6. Yoffe B, Burns DK, Bhatt HS, Combes B. Extrahepatic hepatitis B virus DNA sequences in patients with acute hepatitis B infection. *Hepatology*. 1990;12(2):187-92.
7. Brind A, Jiang J, Samuel D, et al. Evidence for selection of hepatitis B mutants after liver transplantation through peripheral blood mononuclear cell infection. *J Hepatol*. 1997;26(2):228-35.
8. Feray C, Zignego AL, Samuel D, et al. Persistent hepatitis B virus infection of mononuclear blood cells without concomitant liver infection. The liver transplantation model. *Transplantation*. 1990;49(6):1155-8.
9. Samuel D, Muller R, Alexander G, et al. Liver transplantation in European patients with the hepatitis B surface antigen. *N Engl J Med*. 1993;329(25):1842-7.
10. Ilan Y, Galun E, Nagler A, Baruch

- Y, Livni N, Tur-Kaspa R. Sanctuary of hepatitis B virus in bone-marrow cells of patients undergoing liver transplantation. *Liver Transpl Surg.* 1996;2(3):206-10.
11. Coffin CS, Mulrooney-Cousins PM, Peters MG, et al. Molecular characterization of intrahepatic and extrahepatic hepatitis B virus (HBV) reservoirs in patients on suppressive antiviral therapy. *J Viral Hepat.* 2011;18(6):415-23.
12. Roche B, Feray C, Gigou M, et al. HBV DNA persistence 10 years after liver transplantation despite successful anti-HBs passive immunoprophylaxis. *Hepatology.* 2003;38(1):86-95.
13. Marzano A, Gaia S, Ghisetti V, et al. Viral load at the time of liver transplantation and risk of hepatitis B virus recurrence. *Liver Transpl.* 2005;11(4):402-9.
14. Tur-Kaspa R, Laub O. Corticosteroids stimulate hepatitis B virus DNA, mRNA and protein production in a stable expression system. *J Hepatol.* 1990;11(1):34-6.
15. Prieto M, Gomez MD, Berenguer M, et al. 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(1):51-8.
16. Dodson SF, Issa S, Araya V, et al. Infectivity of hepatic allografts with antibodies to hepatitis B virus. *Transplantation.* 1997;64(11):1582-4.
17. Chen YS, Wang CC, de Villa VH, et al. Prevention of de novo hepatitis B virus infection in living donor liver transplantation using hepatitis B core antibody positive donors. *Clin Transplant.* 2002;16(6):405-9.
18. Gow PJ, Mutimer DJ. De novo hepatitis B infection acquired during liver transplantation. *Qjm.* 2001;94(5):271-5.
19. Celebi Kobak A, Karasu Z, Kilic M, et al. Living donor liver transplantation from hepatitis B core antibody positive donors. *Transplant Proc.* 2007;39(5):1488-90.
20. Rosenau J, Bahr MJ, Tillmann HL, et al. Lamivudine and low-dose hepatitis B immune globulin for prophylaxis of hepatitis B reinfection after liver transplantation possible role of mutations in the YMDD motif prior to transplantation as a risk factor for reinfection. *J Hepatol.* 2001;34(6):895-902.
21. Carman WF, Trautwein C, van Deursen FJ, et al. Hepatitis B virus envelope variation after transplantation with and without hepatitis B immune globulin prophylaxis. *Hepatology.* 1996;24(3):489-93.
22. Trautwein C, Schrem H, Tillmann HL, et al. Hepatitis B virus mutations in the pre-S genome before and after liver transplantation. *Hepatology.* 1996;24(3):482-8.
23. Abdelmalek MF, Pasha TM, Zein NN, Persing DH, Wiesner RH, Douglas DD. Subclinical reactivation of hepatitis B virus in liver transplant recipients with past exposure. *Liver Transpl.* 2003;9(12):1253-7.
24. McMillan JS, Shaw T, Angus PW, Locarnini SA. Effect of immunosuppressive and antiviral agents on hepatitis B virus replication in vitro. *Hepatology.* 1995;22(1):36-43.
25. Tur-Kaspa R, Shaul Y, Moore DD, et al. The glucocorticoid receptor recognizes a specific nucleotide sequence in hepatitis B virus DNA causing increased activity of the HBV enhancer. *Virology.* 1988;167(2):630-3.
26. Douglas DD, Rakela J, Wright TL, Krom RA, Wiesner RH. The clinical course of transplantation-associated de novo hepatitis B infection in the liver transplant recipient. *Liver Transpl Surg.* 1997;3(2):105-11.
27. Roche B, Samuel D, Gigou M, et al. De novo and apparent de novo hepatitis B virus infection after liver transplantation. *J Hepatol.* 1997;26(3):517-26.
28. Castells L, Vargas V, Rodriguez F, et al. Clinical impact and efficacy of lamivudine therapy in de novo hepatitis B infection after liver transplantation. *Liver Transpl.* 2002;8(10):892-900.
29. Chazouilleres O, Mamish D, Kim M, et al. "Occult" hepatitis B virus as source of infection in liver transplant recipients. *Lancet.* 1994;343(8890):142-6.
30. Gonzalez-Peralta RP, Andres JM, Tung FY, et al. Transplantation of a hepatitis B surface antigen-positive donor liver into a hepatitis B virus-negative recipient. *Transplantation.* 1994;58(1):114-6.
31. Dickson RC, Everhart JE, Lake JR, et al. Transmission of hepatitis B by transplantation of livers from donors positive for antibody to hepatitis B core antigen. The National Institute of Diabetes and Digestive and Kidney Diseases Liver Transplantation Database. *Gastroenterology.* 1997;113(5):1668-74.
32. Wachs ME, Amend WJ, Ascher NL, et al. The risk of transmission of hepatitis B from HBsAg(-), HBcAb(+), HBIgM(-) organ donors. *Transplantation.* 1995;59(2):230-4.
33. Uemoto S, Sugiyama K, Marusawa H, et al. Transmission of hepatitis B virus from hepatitis B core antibody-positive donors in living related liver transplants. *Transplantation.* 1998;65(4):494-9.
34. Munoz SJ. Use of hepatitis B core antibody-positive donors for liver transplantation. *Liver Transpl.* 2002;8(10 Suppl 1):S82-7.
35. Ghany MG, Ayola B, Villamil FG, et al. Hepatitis B virus S mutants in liver transplant recipients who were reinfected despite hepatitis B immune globulin prophylaxis. *Hepatology.* 1998;27(1):213-22.
36. Huang EJ, Wright TL, Lake JR, Combs C, Ferrell LD. Hepatitis B and C coinfections and persistent hepatitis B infections: clinical outcome and liver pathology after transplantation. *Hepatology.* 1996;23(3):396-404.
37. Ghisetti V, Marzano A, Zamboni F, et al. Occult hepatitis B virus infection in HBsAg negative patients undergoing liver transplantation: clinical significance. *Liver Transpl.* 2004;10(3):356-62.
38. Marusawa H, Uemoto S, Hijikata M, et al. Latent hepatitis B virus infection in healthy individuals with antibodies to hepatitis B core antigen. *Hepatology.* 2000;31(2):488-95.
39. Grellier L, Mutimer D, Ahmed M, et al. Lamivudine prophylaxis against reinfection in liver transplantation for hepatitis B cirrhosis. *Lancet.* 1996;348(9036):1212-5.
40. Yao FY, Osorio RW, Roberts JP, et al. Intramuscular hepatitis B immune globulin combined with lamivudine for prophylaxis against hepatitis B recurrence after liver transplantation. *Liver Transpl Surg.* 1999;5(6):491-6.
41. Sawyer RG, McGory RW, Gaffey MJ, et al. Improved clinical outcomes with liver transplantation for hepatitis B-induced chronic liver failure using passive immunization. *Ann Surg.* 1998;227(6):841-50.
42. Cholongitas E, Vasiliadis T, Antoniadis N, Goulis I, Papanikolaou V, Akriviadis E. Hepatitis B prophylaxis post liver transplantation with newer nucleos(t)ide analogues after hepatitis B immunoglobulin discontinuation. *Transpl Infect Dis.* 2012;14(5):479-487.
43. Daude M, Rostaing L, Saune K, et al. Tenofovir therapy in hepatitis B virus-positive solid-organ transplant recipients. *Transplantation.* 2011;91(8):916-20.
44. Perrillo RP, Wright T, Rakela J, et al. A multicenter United States-Canadian trial to assess lamivudine monotherapy before and after liver transplantation for chronic hepatitis B. *Hepatology.* 2001;33(2):424-32.
45. Mutimer D, Dusheiko G, Barrett C, et al. Lamivudine without HBIg for prevention of graft reinfection by hepatitis B: long-term follow-up. *Transplantation.* 2000;70(5):809-15.
46. Zheng S, Chen Y, Liang T, et al. Prevention of hepatitis B recurrence after liver transplantation using lamivudine or lamivudine combined with hepatitis B Immunoglobulin prophylaxis. *Liver Transpl.* 2006;12(2):253-8.
47. Jiao ZY, Jiao Z. Prophylaxis of recurrent hepatitis B in Chinese patients after liver transplantation using lamivudine combined with hepatitis B immune globulin according to the titre of antibody to hepatitis B surface antigen. *Transplant*

48. Xiong X, Flores C, Yang H, Toole JJ, Gibbs CS. Mutations in hepatitis B DNA polymerase associated with resistance to lamivudine do not confer resistance to adefovir in vitro. *Hepatology*. 1998;28(6):1669-73.

49. Perrillo R, Schiff E, Yoshida E, et al. Adefovir dipivoxil for the treatment of lamivudine-resistant hepatitis B mutants. *Hepatology*. 2000;32(1):129-34.

50. Schiff ER, Lai CL, Hadziyannis S, et al. Adefovir dipivoxil therapy for lamivudine-resistant hepatitis B in pre- and post-liver transplantation patients. *Hepatology*. 2003;38(6):1419-27.

51. Schilling R, Ijaz S, Davidoff M, et al. Endocytosis of hepatitis B immune globulin into hepatocytes inhibits the secretion of hepatitis B virus surface antigen and virions. *J Virol*. 2003;77(16):8882-92.

52. Fung J, Cheung C, Chan SC, et al. Entecavir monotherapy is effective in suppressing hepatitis B virus after liver transplantation. *Gastroenterology*. 2011;141(4):1212-9.

53. König V, Hopf U, Neuhaus P, et al. Long-term follow-up of hepatitis B virus-infected recipients after orthotopic liver transplantation. *Transplantation*. 1994;58(5):553-9.

54. Johnson PJ, Wansbrough-Jones MH, Portmann B, et al. Familial HBsAg-positive hepatoma: treatment with orthotopic liver transplantation and specific immunoglobulin. *Br Med J*. 1978;1(6107):216.

55. Samuel D, Bismuth A, Mathieu D, et al. Passive immunoprophylaxis after liver transplantation in HBsAg-positive patients. *Lancet*. 1991;337(8745):813-5.

56. McGory RW, Ishitani MB, Oliveira WM, et al. Improved outcome of orthotopic liver transplantation for chronic hepatitis B cirrhosis with aggressive passive immunization. *Transplantation*. 1996;61(9):1358-64.

57. 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(2):206-10.

58. Degertekin B, Han SH, Keeffe EB, et al. Impact of virologic breakthrough and HBIG regimen on hepatitis B recurrence after liver transplantation. *Am J Transplant*. 2010;10(8):1823-33.

59. 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(8):955-62.

60. Angelico M, Di Paolo D, Trinito MO, et al. Failure of a reinforced triple course

of hepatitis B vaccination in patients transplanted for HBV-related cirrhosis. *Hepatology*. 2002;35(1):176-81.

61. Sanchez-Fueyo A, Rimola A, Grande L, et al. Hepatitis B immunoglobulin discontinuation followed by hepatitis B virus vaccination: A new strategy in the prophylaxis of hepatitis B virus recurrence after liver transplantation. *Hepatology*. 2000;31(2):496-501.

62. Yoshida EM, Erb SR, Partovi N, et al. Liver transplantation for chronic hepatitis B infection with the use of combination lamivudine and low-dose hepatitis B immune globulin. *Liver Transpl Surg*. 1999;5(6):520-5.

63. 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(4):429-33.

64. Marzano A, Salizzoni M, Debernardi-Venon W, et al. Prevention of hepatitis B virus recurrence after liver transplantation in cirrhotic patients treated with lamivudine and passive immunoprophylaxis. *J Hepatol*. 2001;34(6):903-10.

65. Samuel D, Bismuth A, Serres C, et al. HBV infection after liver transplantation in HBsAg positive patients: experience with long-term immunoprophylaxis. *Transplant Proc*. 1991;23(1 Pt 2):1492-4.

66. Dodson SF, de Vera ME, Bonham CA, Geller DA, Rakela J, Fung JJ. Lamivudine after hepatitis B immune globulin is effective in preventing hepatitis B recurrence after liver transplantation. *Liver Transpl*. 2000;6(4):434-9.

67. Buti M, Mas A, Prieto M, et al. A randomized study comparing lamivudine monotherapy after a short course of hepatitis B immune globulin (HBIG) and lamivudine with long-term lamivudine plus HBIG in the prevention of hepatitis B virus recurrence after liver transplantation. *J Hepatol*. 2003;38(6):811-7.

68. Saab S, Waterman B, Chi AC, Tong MJ. Comparison of different immunoprophylaxis regimens after liver transplantation with hepatitis B core antibody-positive donors: a systematic review. *Liver Transpl*. 2010;16(3):300-7.

69. 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(5):1460-6.

70. Neff GW, Kemmer N, Kaiser TE, et al. Combination therapy in liver transplant recipients with hepatitis B virus without hepatitis B immune globulin. *Dig Dis Sci*. 2007;52(10):2497-500.

71. Hellinger WC, Bonatti H, Yao JD, et al. Risk stratification and targeted antifungal prophylaxis for prevention of aspergillosis and other invasive mold infections after liver transplantation. *Liver Transpl*. 2005;11(6):656-62.

72. Stravitz RT, Shiffman ML, Kimmel M, et al. Substitution of tenofovir/emtricitabine for Hepatitis B immune globulin prevents recurrence of Hepatitis B after liver transplantation. *Liver Int*. 2013;32(7):1138-45.

73. Fox AN, Terrault NA. The option of HBIG-free prophylaxis against recurrent HBV. *J Hepatol*. 2012;56(5):1189-97.

74. Loomba R, Rowley AK, Wesley R, et al. Hepatitis B immunoglobulin and Lamivudine improve hepatitis B-related outcomes after liver transplantation: meta-analysis. *Clin Gastroenterol Hepatol*. 2008;6(6):696-700.

75. Hawkins AE, Gilson RJ, Gilbert N, et al. Hepatitis B virus surface mutations associated with infection after liver transplantation. *J Hepatol*. 1996;24(1):8-14.

76. Protzer-Knolle U, Naumann U, Bartenschlager R, et al. Hepatitis B virus with antigenically altered hepatitis B surface antigen is selected by high-dose hepatitis B immune globulin after liver transplantation. *Hepatology*. 1998;27(1):254-63.

77. Lo CM, Liu CL, Chan SC, Lau GK, Fan ST. Failure of hepatitis B vaccination in patients receiving lamivudine prophylaxis after liver transplantation for chronic hepatitis B. *J Hepatol*. 2005;43(2):283-7.

78. Bienzle U, Gunther M, Neuhaus R, Neuhaus P. Successful hepatitis B vaccination in patients who underwent transplantation for hepatitis B virus-related cirrhosis: preliminary results. *Liver Transpl*. 2002;8(6):562-4.

79. Bihl F, Russmann S, Gurtner V, et al. Hyperimmune anti-HBs plasma as alternative to commercial immunoglobulins for prevention of HBV recurrence after liver transplantation. *BMC Gastroenterol*. 2010;10:71.

80. Di Costanzo GG, Lanza AG, Picciotto FP, et al. Safety and efficacy of subcutaneous hepatitis B immunoglobulin after liver transplantation: an open single-arm prospective study. *Am J Transplant*. 2013;13(2):348-52.

81. Yahyazadeh A, Beckebaum S, Cicinnati V, et al. Efficacy and safety of subcutaneous human HBV-immunoglobulin (Zutectra) in liver transplantation: an open, prospective, single-arm phase III study. *Transpl Int*. 2011;24(5):441-50.

82. Singham J, Greanya ED, Lau K, Erb SR, Partovi N, Yoshida EM. Efficacy of maintenance subcutaneous hepatitis B immune globulin (HBIG) post-transplant for prophylaxis against hepatitis B recurrence. *Ann Hepatol*. 2010;9(2):166-71.

83. Yi NJ, Choi JY, Suh KS, et al. Post-transplantation sequential entecavir monotherapy following 1-year combination therapy with hepatitis B immunoglobulin. *J Gastroenterol.* 2013 Mar 6. (Accession number 23463400)
84. Shouval D, Samuel D. Hepatitis B immune globulin to prevent hepatitis B virus graft reinfection following liver transplantation: a concise review. *Hepatology.* 2000;32(6):1189-95.
85. Locarnini SA. Hepatitis B virus surface antigen and polymerase gene variants: potential virological and clinical significance. *Hepatology.* 1998;27(1):294-7.
86. Roche B, Roque-Afonso AM, Sebah M, et al. 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(7):885-94.
87. Chung RT, Feng S, Delmonico FL. Approach to the management of allograft recipients following the detection of hepatitis B virus in the prospective organ donor. *Am J Transplant.* 2001;1(2):185-91.
88. Nery JR, Nery-Avila C, Reddy KR, et al. 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(8):1179-86.