Hepatitis B virus infection and renal transplantation

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Abstract
Although the prevalence of chronic hepatitis B virus (HBV) infection has declined in renal transplant recipients (RTRs), it remains a relevant clinical problem with high morbidity and mortality in long-term follow up. A thorough evaluation, including liver biopsy as well as assessment of HBV replication in serum (i.e. hepatitis B e antigen and/or HBV DNA) is required before transplantation. Interferon should not be used in this setting because of low efficacy and precipitation on acute allograft rejection. The advent of effective antiviral therapies offers the opportunity to prevent the progression of liver disease after renal transplantation. However, as far as we are aware, no studies have compared prophylactic and preemptive strategies. To date, the majority of RTRs with HBV-related liver disease have had a high virological and biochemical response to lamivudine use. However, lamivudine resistance is frequent with a prolonged course of therapy. Considering long-term treatment, antiviral agents with a high genetic barrier to resistance and lack of nephrotoxicity are suggested. The optimal strategy in RTRs with HBV infection remains to be established in the near future.

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Key words: Hepatitis B; Renal transplantation; Lamivudine resistance

INTRODUCTION
Since the first successful renal transplantation in 1954, there has been an exponential growth in publications dealing with the care of renal transplant recipients (RTRs). Hepatitis B virus (HBV) infection is an established cause of morbidity and mortality in RTRs. Although numerous studies have reported the impact of HBV status on patients and graft outcome in RTRs, the role in pathogenesis of liver damage is still unclear. In recent decades, as improvement in renal transplantation has been the result of better immunosuppression, organ preservation, and patient selection. In addition, substantial improvement in the understanding of HBV virology and the natural course of infection, combined with highly sensitive HBV DNA assays and the advent of effective antiviral drugs with different mechanisms of action, has led to better therapeutic strategies for chronic HBV infection.
increasing interest to determine the long-term outcome of HBV in RTRs. Hence, the aim of this study is to review the available literature concerning the natural course and clinical manifestations of HBV-related liver disease in RTRs. Furthermore, treatment of RTRs with HBV infection is discussed.

PREVALENCE RATES OF HBV INFECTION IN RTRs

The prevalence rates of hepatitis B surface antigen (HBsAg) seropositive status among RTRs varies among countries (Table 1), and it has been decreasing over time[3-7]. Mathurin and colleagues have reported that the prevalence of HBsAg decreased significantly (24.2% before 1982 vs 9.1% after 1982, P < 0.001)[3]. Recently, Santos et al[9] also have shown a marked decline in the prevalence of HBV infections over the last 15 years (6.2% in 1994 vs 2.3% in 2006). In our previous study[3], the prevalence of HBV infection in RTRs was 9.2% (51/554), which is lower than that reported previously in Taiwan in 1994 (20.9%), 1982 (14.7%)[10]. The decreasing prevalence of HBV infection in this population can be attributed to the use of HBV vaccination, the use of erythropoietin for anemia and the consequent decreased need for blood transfusions during the pre-transplantation period.

TRANSMISSION OF HBV INFECTION BY RENAL TRANSPLANTATION: DONOR EVALUATION

The possibility of HBV transmission by organ transplantation can be predicted from the serological status of both donor and recipient. It is generally accepted that transplanting an HBsAg-positive allograft into an HBsAg-negative recipient carries a significant risk of de novo infection[11,12]. A recent meta-analysis has shown that recipients who are seropositive for HBsAg show an increased risk for mortality and graft failure compared with seronegative recipients[3]. This has resulted in a policy at many organ procurement organizations to restrict the use of kidneys from HBsAg-positive deceased donors. However, the rapid increase in patients with end-stage renal disease has exacerbated the shortage of donor organs. The ban on using kidneys from HBsAg-positive donors has been challenged under certain circumstances. A study from Thailand[13] has reported that 14 anti-HBsAg-positive patients received kidneys from HBsAg-positive donors and 27 HBsAg-positive patients received kidneys from HBsAg-negative donors. Hepatitis B hyperimmune globulin (HBIG) and lamivudine were not used at any time. The 10-year survival of these patients was not significantly different (92.8% vs 62.5%, P = 0.14). In a study from Turkey, Berber et al[7] have reported seven kidney transplants from HBsAg-positive donors. All of the recipients were HBsAg-negative and hepatitis B surface antibody (HBsAb)-positive. Prophylactic lamivudine treatment after transplantation was given. None of the patients who received a kidney from an HBsAg-positive donor developed clinical HBV infection in a mean 42-mo follow-up period. Jiang et al[14] have reported a prospective non-randomized controlled study: 373 HBsAg-positive RTRs received a kidney from HBsAg-positive (n = 65) or HBsAg-negative (n = 308) donors. Using a standardized immunosuppressive and antiviral regimen (400 U HBIG once and twice for recipients with HBsAg-negative or HBsAg-positive grafts, respectively; 400 U HBIG weekly for 3 mo and lamivudine 100 mg daily for 6 mo for recipients with HBV DNA-positive grafts), there was no significant difference in liver injury and patient survival. Therefore, it is suggested that kidney allografts from HBsAg-positive donors can be used safely in HBsAb-positive recipients with preexisting naturally acquired or vaccination-induced immunity to HBV. HBV viral status should be monitored, and HBIG and/or lamivudine should be prescribed, depending on donor HBV DNA status.

Table 1  Frequency of hepatitis B surface antigen-positivity in renal transplant recipients

| Authors            | HBsAg rate, % (n) | Reference year | Country of origin |
|--------------------|-------------------|----------------|------------------|
| Hu et al[10]       | 20.9 (14/67)      | 1994           | Taiwan (China)   |
| Mathurin et al[10] | 15.3 (128/834)    | 1999           | France           |
| Lee et al[10]      | 12.9 (62/477)     | 2001           | Taiwan (China)   |
| Chan et al[10]     | 13.2 (67/509)     | 2002           | Hong Kong (China) |
| Morales et al[9]   | 2.2 (76/3365)     | 2004           | Spain            |
| Aroldi et al[3]    | 14.2 (77/541)     | 2005           | Italy            |
| Santos et al[3]    | 3 (37/1224)       | 2009           | Portugal         |
| Tsai et al[3]      | 9.2 (51/554)      | 2009           | Taiwan (China)   |

Table 1-Frequency of hepatitis B surface antigen-positivity in renal transplant recipients

1 Prevalence of hepatitis B surface antigen (HBsAg) was 24.2% before 1982 and 9.1% after 1982 (P < 0.001). Prevalence of HBsAg was 3.0% in 1990 and 2.0% in 1996. Prevalence of HBsAg was 6.2% in 1994, 4.1% in 1998, 3.2% in 2002, and 2.3% in 2006.

NATURAL HISTORY OF HBV DISEASE IN RTRs

Defining the natural history of HBV infection among RTRs is difficult because of the unique characteristics of this population and chronic HBV infection has a long natural course, and it might need 10-20 years to see the key complications, most notably cirrhosis and hepatocellular carcinoma (HCC). The natural history of hepatitis B in the immunocompetent population has been described by Liaw et al[15]. Chronic HBV infection is a dynamic state of interactions between HBV, hepatocytes and the immune system of the patient. Therefore, the natural course of chronic HBV infection can be divided into four phases: immune tolerant, immune clearance, residual inactive, and reactive immune clearance phases. The reactive phase can be viewed as a variant of the immune clearance phase. However, in the population of RTRs, therapeutic immunosuppression post-transplantation might affect the host immune responses against HBV. In addition, most centers are reluctant to perform liver biopsies before and after renal transplantation due to concern about platelet...
dysfunction. Furthermore, antiviral therapy is now widely available, which might change the course of hepatitis and stop disease progression. All these factors limit the clinician's understanding of the progression of liver disease in RTRs.

Fornairon et al. have reported a large cohort study of 151 HBsAg-positive RTRs. The spontaneous annual clearance rates of HBsAg, hepatitis e antigen (HBeAg), and HBV DNA were 0.1%, 3%, and 3%, respectively, which are lower than in the general population. A high rate of persistent viral replication and reactivation, as defined by HBeAg reappearance, was observed in 30% after renal transplantation, which was significantly higher than in the general population. Degos et al. have demonstrated reactivation of HBV replication in 11 of 12 (92%) initially HBV-DNA-negative, HBsAg-positive RTRs after 3-12 mo and an increase in HBV DNA in 6 of 11 (55%) initially HBV-DNA-positive patients. In our study of 51 HBsAg-positive RTRs during a mean follow-up of 58 mo, 34 patients (67%) had higher HBV DNA levels at the end of follow-up than at baseline, which was associated with cirrhosis development.

Liver biopsy is a gold standard for the diagnosis of hepatic disease. A variety of studies has shown more severe courses in RTRs infected with HBV compared with non-infected patients. In 1985, Parfrey et al. performed a prospective study of 20 HBsAg-positive RTRs who underwent serial liver biopsy. There was a marked tendency to progression, and 82% of patients who had virus only, reactive hepatitis, or chronic persistent hepatitis on initial biopsy, subsequently developed chronic active hepatitis or cirrhosis on final biopsy. Fornairon et al. have reported the largest single-center evaluation of follow-up liver biopsies in HBsAg-positive RTRs: 310 biopsies in 131 RTRs, with two or more biopsies in 101 patients. At the time of renal transplantation, normal liver histology was found in 39%, chronic persistent hepatitis in 25%, chronic active hepatitis in 25%, and miscellaneous findings in 11% of patients. After a mean interval of 66 mo, histological deterioration was observed in 85.3% of these 101 patients who underwent serial liver biopsies, with occurrence of cirrhosis in 28% and chronic active hepatitis in 42%. Only 6% showed normal liver biopsy in the second biopsy. These results were in accordance with the findings in other smaller series. Aroldi et al. have reported 34 HBsAg-positive RTRs who underwent serial liver biopsy: 24 (71%) showed progression of liver fibrosis in which 15 patients evolved to cirrhosis, and six of them died of liver failure.

The reactivation of HBV infection in RTRs can also occur in HBsAg-negative but HBeA- and hepatitis B core antibody (HBeAb)-positive patients. However, it is difficult to distinguish these from de novo infection. There have also been a few reports in the literature about the reactivation of HBV infection in RTRs with previously resolved HBV infection. Blanpain et al. have reported two RTRs with cured HBV infection at the time of transplantation, as defined by the absence of HBsAg and the presence of HBeAb and HBcAb in the serum, who presented with HBV reactivation at 7 mo and 3 years after transplantation, respectively. Degos et al. have detected HBV DNA in seven of 35 RTRs (20%) following transplantation, who either had no serological evidence of HBsAg or HBV DNA before transplantation; a finding that suggests that immunosuppression can amplify even minimal residual HBV DNA. Based on this evidence, transplant physicians should be aware of the risk of HBV reactivation in patients with cured HBV infection before transplantation.

**OUTCOME OF RTRs WITH HBV INFECTION: MORTALITY AFTER TRANSPLANTATION**

Mortality is a reliable end-point in the natural course of HBV after renal transplantation. However, the impact of HBsAg on survival in RTRs has been controversial, especially in early studies. Some initial studies that have focused on 5-year survival rates generally have failed to show a difference between HBsAg-positive and -negative RTRs. However, more recent studies with a large sample size and longer follow-up have suggested a detrimental effect of HBsAg on patient and graft survival. Lee et al. have reported that the 10-year survival rate was much higher in the HBsAg-negative group (82.8%) than in the HBsAg-positive group (51.4%) (P < 0.005). Multivariate analysis has revealed that HBV infection is an independent risk factor for patient mortality. The major cause of death was liver failure in the HBsAg-positive group: 62.5% (10/16) vs 23.3% (7/30) in the HBsAg-negative group. Mathurin and colleagues also have reported that 10-year survival was significantly higher in non-infected (80% ± 3%) than in HBsAg-positive recipients (55% ± 6%). Multivariate analysis has shown that, in patients transplanted before 1982 (year of HBV vaccination), HBsAg was an independent factor for poor survival (P < 0.001). In a case-control study by Mathurin, survival was significantly lower at 10 years in patients infected by HBV than in matched patients (55% ± 6% vs 80% ± 4%, P = 0.004). Furthermore, in a study by Chan from Hong Kong, HBsAg-positive patients who underwent renal transplantation before 1996, without the availability of lamivudine, had a markedly inferior survival rate compared with that in HBsAg-negative RTRs. Recently, a meta-analysis performed by Fabrizi et al., which pooled 6050 patients, indicated clearly that HBsAg in serum was an independent risk factor for death after renal transplantation (relative risk: 2.49, P < 0.0001).

**OUTCOME IN RTRs WITH HBV INFECTION: MORBIDITY AFTER TRANSPLANTATION**

**Graft survival**

The influence of chronic HBV infection on graft survival remains controversial. In a large cohort study by Foraniron, better allograft survival was described in HBsAg-
positive than in HBsAg-negative patients ($P = 0.0006$). Also London $et$ $al$\cite{31} have found a beneficial effect of HBsAg positivity on graft survival. In contrast, Lee $et$ $al$\cite{35} have reported an inferior 10-year graft survival for HBV- or hepatitis C virus (HCV)-infected RTRs, although this was not significant (44% and 50%, $P = NS$, respectively) compared with non-infected patients (74%). Recently, Mathurin $et$ $al$\cite{38} have observed that 10-year graft survival (36%) in HBsAg-positive RTRs was significantly lower compared with that in non-infected patients (63%). Their case-control study also showed that 10-year graft survival was significantly lower in patients infected by HBV than in matched control patients (36% ± 5% vs 61% ± 5%, $P < 0.0001$). Finally, a 2005 meta-analysis has indicated that HBsAg positivity was associated with an increased risk of allograft loss (relative risk: 1.44, 95% CI: 1.02-2.04)\cite{39}.

### FACTORS AFFECTING PROGRESSION IN HBV-RELATED DISEASE AFTER RENAL TRANSPLANTATION

In chronic HBV patients, viral factors (viral load, genotype and genomic mutations), host factors (age, sex, and immune status), and other factors (alcohol consumption, cigarette smoking, exposure to aflatoxin, and other viral superinfections) contribute to the progression of liver disease\cite{32}. However, in RTRs with HBV infection, the factors that affect HBV-related progression have not been identified. Fairley $et$ $al$\cite{39} have found that the presence of HBV DNA and/or HBsAg in serum prior to renal transplantation was associated with an increased probability of death from liver disease: five of 10 patients in this group died of chronic liver disease; but only one of 15 patients who were HBsAg and/or HBsAg negative prior to transplantation died of liver disease ($P = 0.002$). In our previous study\cite{39}, 13 of 51 RTRs developed cirrhosis in a period of 57 mo. Among these, HBV DNA levels at baseline could not predict cirrhosis development. However, the elevation of serum HBV DNA ($\geq 10^5$ copies/mL) after renal transplantation was a significant risk factor for development of cirrhosis.

There are at least eight major genotypes of HBV (A-H) with distinct geographical distribution. Genotype A and C variants can induce more severe liver disease than genotype B and D in general immunocompetent chronic HBV patients\cite{34,36}. To date, a paucity of data exists to discuss the HBV genotype that affects liver disease in RTRs. Only our previous study has demonstrated that there is no significant association between genotype and cirrhosis development in RTRs\cite{39}. We do not know the reason for this inconsistency with results from general chronic HBV populations. However, genotype B was the predominant genotype in the RTRs (45/51, 88.2%) of our study, which is considerably higher than that (60%) in the general population\cite{39}. This difference might have been because these patients were selected before renal transplantation for their relatively benign clinical course of hepatitis B.

Chu $et$ $al$\cite{40} have suggested that older RTRs with HBsAg and/or HCV antibody carriers have a greater chance of developing HCC and mortality than younger patients do. In that study, 173 RTRs with serum HBsAg and/or HCV antibody were divided into three groups: older age ($\geq 55$ years, $n = 3$); middle age (18-55 years, $n = 160$); and younger age ($\leq 18$ years, $n = 10$). The incidence of HCC and the risk of death due to liver disease post-transplantation in the older, middle and younger age groups were 100%, 3.75% and 0% ($P < 0.001$), and 100%, 19.8% and 0% ($P < 0.001$) respectively. These results were in agreement with the findings from the study of Arolf\cite{41}, in which older age (40 years) was independently associated with poor survival in RTRs (relative risk: 2.8).

Recent studies have indicated that precore and core promoter mutations are significantly associated with advanced liver disease in chronic HBV carriers\cite{39,41-44}. For immunosuppressed patients, Günther $et$ $al$\cite{45} have performed serial HBV sequences by polymerase chain reaction (PCR) and DNA sequencing in nine HBsAg-positive RTRs. Seven of them showed either persistent or increasing amounts of the HBV core gene deletion mutants. All seven patients developed cirrhosis, and five died from end-stage liver disease. The incidence of complications was higher than in recipients without mutations. In our previous analysis\cite{9}, there was no significant association between core promoter mutations (T1762/A1764) and advanced liver disease. However, we have found that the development of T1762/A1764 mutants can predict an increase in HBV DNA, which was associated with cirrhosis development after renal transplantation. Hence, we hypothesized that immunosuppressive agents induce HBV DNA replication, especially in recipients with T1762/A1764 mutants and cirrhosis development. In a study by Preikschat $et$ $al$\cite{46}, development of cirrhosis and end-stage liver disease after renal transplantation was associated with persistence and accumulation of specific HBV mutant populations. Their results demonstrate that viruses are characterized by a set of mutations rather than by a single mutation: deletions/insertions in core promoter plus deletion in the C gene and/or deletion in the pre-S region.

### THERAPY OF HEPATITIS B IN RTRs

With the improving results of renal transplantation techniques and care, liver disease has emerged as an important cause of morbidity and mortality. Before the advent of effective antiviral agents, chronic liver disease developed in > 80% of HBsAg-positive RTRs, and 37%-57% of mortality in these subjects was attributed to liver complications\cite{31,33,44}. Therefore, hepatitis B was considered to be a contraindication for organ donation in some western countries in the era before antiviral agents. However, the past decade has witnessed important developments in the therapy of hepatitis B. The availability
of lamivudine in 1998 marked a new era of oral therapy. According the study by Chan et al[57], the survival of HBsAg-positive RTRs treated preemptively with lamivudine was similar to that of HBSAg-negative controls, whereas HBsAg-positive RTRs without lamivudine treatment had significantly inferior survival (relative risk of death: 9.7, \( P < 0.001 \)). A study by Ahn et al[61] has investigated the clinical outcome of 2054 RTRs to establish the efficacy of lamivudine treatment in HBsAg-positive recipients \((n = 66)\). Lamivudine given to 27 recipients markedly improved 10-year patient and graft survival compared to those who did not take lamivudine. Notably, the 10-year patient survival rates were similar between pre-transplant HBsAg-negative and -positive patients (88.2% vs 85.3%). Hence, the overall prognosis of patients with HBsAg positivity has probably improved given the increased efficacy of antiviral therapy. Currently, there are seven agents approved for the treatment of chronic hepatitis B by the US Food and Drug Administration[10,16,47]. They are conventional interferon (IFN)-\(\alpha\), pegylated IFN, lamivudine, adefovir, entecavir, telbivudine and tenofovir. In the non-renal transplant population, IFN-based therapy is modestly efficacious in inducing HBeAg loss or seroconversion (30%-40%) in HBeAg-positive patients[48-51] and entecavir, telbivudine and tenofovir are the most potent in HBV DNA suppression. At 1 year, \(\geq 60\%\) of HBeAg-positive and \(\geq 85\%\) of HBeAg-negative chronic hepatitis B patients achieved undetectable HBV DNA after therapy with these three agents[52-54]. Drug resistance occurs most frequently with lamivudine, followed by telbivudine, adefovir and tenofovir, and is very low with entecavir[52,53,55-59]. However, the optimal antiviral agent for the treatment of RTRs with chronic hepatitis B infection is still unclear because of limited data on the use of these agents in RTRs. Table 2 summarizes antiviral agents used in RTRs with HBV infection.

**IFN**

IFN has antiviral, antiproliferative and immunomodulatory effects, such as increased cytotoxic T lymphocytes and natural killer cell immune response to viral proteins[60-62]. There have been only a few successful studies of monotherapy with IFN in RTRs. Post et al[64] have reported a 38-year-old RTR who developed symptomatic hepatitis. Tests for HBeAg and HBV DNA were both positive. After treatment with 1 MU IFN\(\alpha\) three times weekly for 3 wk, followed by an increase to 3 MU three time weekly for a total of 16 wk, hepatitis clinically resolved, with HBeAg seroconversion and HBV DNA negativity. The renal allograft function remained excellent throughout the course of therapy with IFN. Grotz et al[64] have reported HBsAg positivity in RTRs suffering from hepatitis flare up. Their patient was HBeAg seropositive, with detectable HBV DNA. IFN was given at a dose of 3 MU three times a week for 14 wk. At the end of treatment, HBeAg seroconversion developed, with a decrease in HBV DNA. However, an acute rejection episode occurred after IFN therapy, and renal biopsy revealed acute interstitial alterations. Prednisone was prescribed and renal function recovered. Although IFN therapy has been shown to terminate effectively viral replication in some RTRs with HBV infection, the use of IFN for the treatment of hepatitis B in RTRs has been reported infrequently. Reluctance to use IFN in RTRs could be related to concerns about precipitating acute allograft rejection, direct nephrotoxicity, and tubulointerstitial nephropathy with glomerular alterations, which are frequently irreversible and steroid resistant[65-68]. As a result, IFN should not be used for treating HBV infection in this setting.

### Table 2  Efficacy summary of antiviral monotherapy in renal transplant recipients with hepatitis B virus infection

| Antiviral agent | Authors | Reference year | Patients | Duration (mo) | Biochemical response\(^1\) (%) | Virological response\(^2\) (%) | Resistance (%) |
|----------------|---------|----------------|---------|--------------|-------------------------------|-----------------------------|----------------|
| Lamivudine     | Rostasing et al\[69\] | 1997 | 6 | 6 | 4/5 (80) | 6/6 (100) | 0 |
|                | Jung et al\[70\] | 1998 | 6 | 8 | 6/6 (100) | 6/6 (100) | 0 |
|                | Fontaine et al\[71\] | 2001 | 26 | 16 | NA | 26/26 (100) | 8/26 (31) |
|                | Lee et al\[72\] | 2001 | 13 | 12 | NA | 10/13 (77) | 1/4 (25) |
|                | Park et al\[73\] | 2001 | 10 | 35 | 8/10 (80) | 7/10 (70) | 1/10 (10) |
|                | Chan et al\[74\] | 2002 | 26 | 32 | 14/14 (100) | 26/26 (100) | 11/26 (42) |
|                | Thabut et al\[75\] | 2004 | 14 | 65 | 8/14 (57) | 14/14 (100) | 8/14 (57) |
|                | Kamar et al\[76\] | 2004 | 18 | 37 | 13/18 (72) | 6/18 (33) | 12/18 (67) |
| Adefovir       | Fontaine et al\[77\] | 2005 | 11 (LAM-R) | 15 | 9/11 (82) | 1 (9) | 0 |
| Entecavir      | Kamar et al\[78\] | 2008 | 8 (ADV-R) | 16 | NA | 5/8 (63) | NA |

\(^1\)Biochemical response was calculated as the disappearance of hepatitis B virus (HBV) viremia at the end of the treatment. HBV DNA was quantified in all studies by non-polymerase chain reaction assay (PCR). hybridization techniques with a limit ranging being 5-6 log\(_{10}\) copies/mL, except for the studies by Thabut, Kamar, Gwak and Fontaine (2005) who used a PCR-based assay. LAM-R: Lamivudine-resistance; ADV-R: Adefovir-resistance; NA: Not available.

**References**

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ical prospective cohort studies that included 184 RTRs. The mean overall clearance of HBV DNA and HBeAg was observed in 91% and 27%, respectively; and alanine aminotransferase normalization occurred in 81%, with lamivudine resistance being reported in 18%. Frequency of HBeAg loss and lamivudine resistance was positively associated with increased duration of therapy \( (r = 0.51, P = 0.039; r = 0.620, P = 0.019, \text{respectively}) \).

**Adefovir**

Adefovir has demonstrated safety and efficacy in treatment-naive patients and those with lamivudine-resistant HBV infection \[58,59,90,91\]. Safety and efficacy also have been proven in immunodeficient patients including HIV-positive patients \[58,59\] and after liver transplantation \[86\]. However, nephrotoxicity and Fanconi-like syndrome with phosphaturia and proteinuria were reported when adefovir was evaluated at higher daily doses (30 mg) \[86\]. Of note, adefovir dose must be adjusted in accordance with creatinine clearance in patients with impaired renal function \[86\]. To date, a paucity of studies exists concerning the use of adefovir in RTRs \[90,91\]. Fontaine et al. \[90\] have described the use of adefovir in 12 RTRs with lamivudine-resistant HBV infection. The daily dosage was 10 mg initially and then adjusted based on renal function. After the 12 mo, the median decline in serum HBV DNA was from 8.76 to 2.97 log \(_{10}\) Eq/mL, without virological breakthrough. The efficacy was similar to that reported in the general population. Notably, there has been no experience in the use of adefovir in treatment-naive RTRs with HBV infection.

**Entecavir, telbivudine and tenofovir**

In immunocompetent patients, entecavir, telbivudine and tenofovir are the most potent antiviral agents, followed by lamivudine and then adefovir. Entecavir is associated with the lowest rate of drug resistance (<1%) in 5 years among previous treatment-naive patients \[58,59\], and therefore, might be the preferred treatment, since long-term therapy will be needed in most RTRs. To date, there are no published data concerning the use of entecavir, telbivudine and tenofovir in RTRs. Only one study has demonstrated the efficacy and safety of entecavir in RTRs with HBV infection \[92\]. Eight RTRs, who have become adefovir or lamivudine-resistant, were administered entecavir (0.5-1 mg/d). After a median follow-up of 16.5 mo, there was a significant decrease in HBV DNA viral loss (3.86 to 2.94 log \(_{10}\) copies/mL, \( P = 0.004 \)). Clinical tolerance of entecavir was very good without any rejection episode. Furthermore, there were no statistically significant changes in creatinine level, estimated creatinine clearance, or daily microalbuminuria. Hence, from currently available data, we suggest that entecavir is preferable to lamivudine, to minimize development of potential drug resistance, unless there are concerns about cost or unavailability of entecavir.

**Drug resistance**

Antiviral resistance is defined as the selection of HBV mutations that confer reduced susceptibility to a drug, which results in primary or secondary treatment failure. Clinically, the emergence of drug resistance is indicated by viral breakthrough, which is defined as a >1 log \(_{10}\) increase in serum HBV DNA from nadir in a patient who had an initial virological response. Usually, subsequent biochemical breakthrough or raised alanine aminotransferase (ALT) values occurred in >90% of patients \[93\] with some hepatic decompensation among patients with advanced fibrosis \[94\]. In chronic hepatitis B immunocompetent patients, lamivudine is associated with the highest rate of resistance, reaching nearly 70% after 5 years of continuous therapy \[95\]. Similarly, there was an increasing incidence of lamivudine resistance with longer treatment in RTRs. Thabut et al. \[96\] have reported 14 RTRs with a median of 65 mo of lamivudine therapy. Lamivudine resistance appeared in eight patients (57%). In the study of Kumar \[96\], virological breakthrough was observed in 12/18 (67%) RTRs after 37 mo of lamivudine treatment. Chan et al. \[97\] have reported 29 RTRs who received almost 60 mo of lamivudine therapy; 14 (48.3%) patients developed lamivudine resistance at 10-35 mo. Among these, hepatic flares were observed in 11 (79%). Therefore, in 2007, the concept of a roadmap was set up by an internal group of experienced hepatologists and virologists \[98\]. The panel recommends monitoring of serum HBV DNA levels to identify outcomes of therapy and to reduce the risk of viral resistance. In our analysis (unpublished data), we set forth the roadmap concept into 19 lamivudine-treated RTRs to monitor the efficacy and resistance of lamivudine. At week 24, there were seven patients with inadequate virological response (defined as HBV DNA levels \( > 2000\) IU/mL (\( \geq 4\) log \(_{10}\) copies/mL) at week 24 after antiviral treatment). Three patients developed YMDD mutations at week 52 and therapy was switched to adefovir-based therapy due to virological breakthrough. In the remaining four patients, two developed YMDD mutation at week 104 and shifted to adefovir-based therapy. These results provide a new insight into the roadmap concept for HBV therapy in RTRs.

**Timing of antiviral agent initiation**

There is lack of an algorithm for therapeutic approaches to antiviral treatment in RTRs with HBV infection. Several points remain to be defined regarding the management of HBV-related liver disease after renal transplantation. The first question is the timing of introduction of the antiviral agent. There are two principal approaches to prevent HBV reactivation after renal transplantation: prophylactic and preemptive strategies. To the best of our knowledge, there have been no studies in the renal transplant setting that have compared directly the prophylactic and preemptive approaches. A prophylactic strategy involves the administration of antiviral agents to patients at increased risk of developing HBV reactivation prior to transplantation; a preemptive strategy permits prompt treatment after the detection a marked increase in serum HBV DNA. Chan et al. \[97\] have confirmed that preemptive lamivudine therapy improves survival of RTRs with HBV infection. There is also some evidence that prophylactic
lamivudine might be beneficial in RTRs. Whatever the prophylactic or preemptive strategy, it can be confirmed that salvage treatment after hepatic dysfunction with HBV recurrence is less effective.

Duration of treatment
The next unanswered question is whether lifelong treatment is needed in this special patient group. In the era of lamivudine, prolonged therapy is associated with drug resistance. One study has reported that lamivudine resistance was observed in three of 14 (21%) patients after 1 year of treatment, and in eight of 14 (57%) patients after 2 years. Withdrawal of lamivudine is associated with a high risk of relapse, replication of the wild strain, and liver failure, all of which suggest prolonged therapy is necessary. Rostaing et al. have found that when lamivudine therapy was stopped for four patients after 6 mo, it was associated with a biochemical and virological relapse within the following weeks. However, a study by Chan et al., in which lamivudine was discontinued in 12 low-risk RTRs (> 9 mo therapy, HBV DNA and HBeAg negative, stable immunosuppression) five patients achieved treatment success, with two maintaining undetectable serum HBV DNA for > 18 mo. It seems that discontinuation is safe in selected patients, to minimize the emergence of drug resistance. Recently, Huang et al. have reported that the liver-related mortality rate was not significantly higher in patients who discontinued lamivudine treatment compared with continuously treated patients (both, 0%), in a total of 20 HBsAg-positive transplant recipients (discontinued, n = 9; continued, n = 11). However, these studies all had limitations of small case numbers and short follow-up periods. In the era of adefovir, entecavir, telbivudine and tenofovir, there are only a few studies concerning their efficacy in RTRs with HBV infection. Further large cohort studies with long-term, and/or combination, and/or high-dose antiviral therapy in HBsAg-positive RTRs are required.

Although there are no definite algorithms about antiviral therapy of HBV in RTRs, the 2007 American Association for the Study of Liver Diseases guidelines issued some suggestions. For chronic hepatitis B patients who require immunsuppressive therapy, prophylactic antiviral therapy is recommended for HBV carriers at the onset of a finite course of immunosuppressive therapy. With baseline HBV DNA < 2000 IU/mL, antiviral therapy should be continue for 6 mo after completion of immunosuppressive therapy. In patients with baseline HBV DNA ≥ 2000 IU/mL level, treatment should be continued until the endpoints are reached. However, there is still a lack of direct evidence for these guidelines to be applied in RTR patients.

CONCLUSION
The reported prevalence of chronic HBsAg carriers receiving renal transplantation is lowering, but it is not negligible, especially in endemic areas for HBV infection. HBV confers a high risk of morbidity and mortality in long-term follow up in RTRs. HBsAg-positive donors can be safely used in anti-HBs-positive recipients. To date, there is no optimal strategy for RTRs with HBV infection. Many points remain to be defined (Figure 1). Lamivudine therapy is effective in serological and virological responses in RTRs, and the tolerance is good. However, resistance to lamivudine frequently occurs with prolonged therapy.

Figure 1 Algorithm for renal transplant candidates with hepatitis B virus infection. The font-underline in figure 1 means that there is no optimal strategy for renal transplant recipients (RTRs) with hepatitis B virus (HBV) infection so far, and they remain to be defined. ALT: Alanine aminotransferase; HBeAg: Hepatitis e antigen.
Considering long-term treatment, antiviral agents with a high genetic barrier to resistance and lack of nephrotoxicity (e.g. entecavir) are suggested. Long-term follow-up studies are required in the near future.

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