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Hepatitis B Infection in Renal Disease

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Chronic hepatitis B virus (HBV) infection in renal patients could result from nosocomial transmission and outbreaks in dialysis units. Vaccination, universal precautions, regular virologic screening and segregation policy are important and effective control of HBV infection in hemodialysis unit. Chronic HBV infection poses problem to dialysis patients, their diagnosis, treatment of hepatic complications and pre-transplant management.

This review summarizes the chronic HBV epidemiology, extrahepatic manifestations, management and prevention.

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The hepatitis B virus (HBV) was discovered in 1968; it is transmitted through the usage of contaminated syringes, particularly among drug abusers, blood transfusions, sexual intercourse with HBV-infected partners and finally from infected mothers to their fetuses and newborns[1].

The acute and chronic liver diseases are an important cause of morbidity in chronic hemodialysis patients. The hepatitis B virus infection is one of the most important factors of the liver disease in these patients. It is a serious problem because of the contamination of the infection from both patients and personnel of the dialysis unit.

Hepatitis B in renal failure is long term and significant problem. Finally, there have been few studies of the natural history and therapy of viral hepatitis B in renal failure patients, making a conclusion difficult. We will examine three important questions. First, what is the prevalence of hepatitis B in renal failure? Second, what is the treatment of hepatitis B in renal failure? Third, how to prevent hepatitis B in renal failure[1]?

Prevalence

HBV remains a major problem in the Asia-Pacific region where the prevalence of HBsAg in CAPD (Continuous Ambulatory Peritoneal Dialysis) and hemodialysis patients directly reflects the prevalence in local population (8-20%)[2].

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The availability of serologic testing for HBV since the 1970s made the incidence of this infection among renal failure patients the subject of study for three decades. In 1974, the nationwide incidence of acute HBV infection among hemodialysis (HD) patients was 6.2%, the rates in selected centers was as high as 30%, in the United States[3]. In 1980, the incidence had fallen to 1% and in 1997, the incidence had fallen further to 0.05%. Despite the success of long-standing infection control practices and immunization to prevent HBV infection, transmission in the HD setting remains a problem. In 1994, five HBV outbreaks occurred in HD units in the United States[3].

The prevalence of HBV surface antigen (HBsAg) among HD patients in the United States has fallen from 7.8% in 1976, 3.8% in 1980, and 0.9% in 1997. In Japan, it is 1.6%, Brazil 10%, Hon Kong 10%, Saudi Arabia 11.8% and Taiwan 16.8%[3-7].

Data derived from western European HD patients followed from 1970 to 1980 showed that HBsAg was present in 10.4%[6]. In general, the overall incidence of HBV infection in dialysis patients is decreasing due to vaccination of HBV, implementation of infection control measures, and advent recombinant human erythropoietin.

Extrahepatic Manifestations of Chronic Hepatitis B

Hepatitis B virus (HBV) has been implicated in the pathogenesis of three different glomerular disorders: Membranous glomerulonephritis (MGN), membranoproliferative glomerulonephritis (MPGN), and IgA nephropathy. MGN is the most common renal manifestation seen with HBV infection. The clinical presentation differs in children and adults. In children, nephrotic proteinuria and hematuria are preceded by a prodromal flulike illness. Renal function remains normal, and serum transaminases usually are normal or only slightly elevated. Spontaneous remission within 1 to 2 years in association with seroconversion to positive anti-hepatitis Be antigen is common, and chronic kidney disease (CKD) develops in only a minority of patients. Adults who have MGN usually have a more aggressive course, presenting with proteinuria, nephrotic syndrome, hypertension, acute kidney injury (AKI), and abnormal liver functions. Spontaneous remission is rare. One third of patients develop progressive renal failure, and 10% require renal replacement therapy within 5 years. Kidney biopsy, along with positive serologies (hepatitis Be antigen and hepatitis B surface antigen) confirms the diagnosis of HBV-related MGN.

Treatment is indicated in patients who have severe nephrotic syndrome who do not undergo spontaneous remission within one year. Steroids are of little benefit in the management of MGN and may be harmful by promoting viral replication and delaying hepatitis Be seroconversion. High dose interferon can induce remission in more than 50% of patients. Antiviral therapy with lamivudine decreases proteinuria and delays progression of renal disease. Hepatitis B vaccination prevents this disease.

In summary liver disease frequently is associated with kidney disease secondary to IgA nephropathy and viral glomerulonephritides. Chronic hepatitis B causes MGN and MPGN with or without type 2 cryoglobulinemia. Therapy is aimed at viral eradication using interferon or lamivudine (in hepatitis B)[8-12].

The serum-sickness like "arthritis-dermatitis" prodrome is seen in approximately one-third of patients acquiring HBV. The joint and skin manifestations are varied, but the syndrome spontaneously resolves at the onset of clinical hepatitis with few significant sequelae. Occasionally, arthritis following the acute prodromal infection may persist; however, joint destruction is rare. The association between HBV and mixed essential cryoglobulinemia remain controversial; but a triad of purpura, arthralgias and weakness, which can progress to nephritis, pulmonary disease and generalized vasculitis, has characterized the syndrome. Finally, skin manifestations of HBV infection typically present as palpable purpura.

Therefore, in summary the extrahepatic manifestations of chronic hepatitis B are:

- Polyarteritis nodosa
- Membranous glomerulonephritis (MGN)
- Mesangial proliferative (MesPGN)
- Membranoproliferative (MPGN)
- Serum sickness-like prodrome
- Essential mixed cryoglobulinemia
- Dermatologic manifestations (non-pruritic erythematous and vasculitis)
- Arthritic manifestations (asymmetrical polyarthritis)
- Neurologic manifestations (peripheral neuropathy, Guillain-Barre syndrome)

Treatment

The primary goal of treatment of HBV is complete eradication of the virus. However, it is rarely achieved due to the characteristic of HBV of covalently closed circular DNA and a replication of HBV in the hepatic nuclei. Therefore, the decision to start treatment is relying on active viral replication (HBeAg and/or HBV DNA assays) and active or high liver enzyme (ALT more than 1.5 times upper limit of normal or moderate/severe chronic liver disease on liver biopsy)[13-15].

There are new nucleoside and nucleotide analogues such as Entecavir, Telbivudine, Tenofovir, which are more potent anti-viral agents and have been tried in general population. No data are available in patients with end stage renal-disease (ESRD) or those receiving dialysis.

HBV Management of Infection before Renal Transplantation

Interferon is an antiviral, anti-proliferative and immunomodulatory glycoprotein. It has so far little role in treating patients with ESRD. First, possibly because of drug accumulation as a result of decreased metabolism of interferon-a by renal tubules in uremic patients, side effects such as flu-like symptoms, neutropenia, thrombocytopenia, neuropsychiatric symptoms, anemia and malnutrition commonly occur and have led to cessation of therapy in more than 50% of patients in one study.

Second, there are very little data, in which there was only one anecdotal report about the efficacy of this drug in treating two dialysis patients. The interferon-a is highly dependent on the activity of liver disease as reflected by the serum ALT level and histological

findings, it is doubtful whether reasonable response could be achieved in dialysis patients who have relatively modest serum ALT level and histological inflammatory activities. Nevertheless Pegylated interferon (PEG-INF), especially PEG-INF-a2a is mainly excreted by hepatic route with a larger molecular weight, lower volume of distribution and longer half-life as compared with conventional non-pegylated form.

Patients with end-stage renal disease have less fluctuation in serum level, less drug accumulation and better tolerability. Nevertheless, the HBV genotypes might affect the treatment response, in which genotype A and B were associated with higher HBeAg seroconversion rate as compared with genotypes C and D. HBV seroconversion rate increased from 12% to 24% compared to conventional interferon (INF) in general population.

In controlled clinical trials of patients without end-stage renal disease, lamivudine achieves profound suppression of HBV replication, serum aminotransferases and histologic necro-inflammation during treatment. Pre-transplant Lamivudine therapy should be considered in any renal transplant candidate with chronic hepatitis B (HBsAg elevated ALT, DNA_105 copies/ml. However, less than 10% of HBsAg patients on hemodialysis have an elevated ALT. Because the elimination of lamivudine is renal, the dose should be reduced in patients with end-stage renal disease, see Table1. Dose-related neutropenia has been reported in hemodialysis patients although a causative association with lamivudine could not be proven, see Table 1.

Table 1: Lamivudine Dose in the End Stage Renal Disease

Creatinine Clearance	Daily Dose
>50 mL/min (>0.83 mL/sec/ssa)	100 mg
30-50 mL/min (0.5-0.83 mL/sec/ssa)	50 mg
15-30 mL/min (0.25-0.5mL/sec/ssa)	25 mg
5-15 mL/min (0.09 -0.25 mL/sec/ssa)	15 mg
<5 mL/min (<0.09mL/sec/ssa)	10 mg

Those HBsAg and HCV candidates who do undergo renal transplantation should be monitored closely for evidence of reactivation. Unfortunately, Interferon has poor efficacy and tolerability in both HBsAg and HCV renal transplant recipients and may precipitate renal allograft rejection. In contrast, lamivudine therapy produces safe and effective suppression of chronic HBV infection in HBsAg transplant recipients. Routine lamivudine prophylaxis begun at the time of transplantation may prevent severe HBV reactivation[16].

Therefore, management of patients with hepatitis B dialysis pending kidney transplantation should be regularly monitored by detailed history, examination and investigations including blood tests and ultrasound. Liver biopsy should be done if there is unexplained elevation in serum ALT or there is an evidence of active liver disease even if serum ALT level is normal. Lamivudine should be given in an adjusted renal dose for patients with significant liver disease and renal impairment[14].

Management of HBV Infection after Renal Transplantation

HBsAg positivity has been a poor prognostic factor for renal transplant due to the common occurrence of hepatitis B reactivation post-transplant, in 70-90% of patients, may be related to the use of immunosuppressive agents[1]. The 10-year survival of HBsAg positive renal transplant patient was once reported to be 55%, but it is 80% in HBsAg negative recipients[16].

Antiviral nucleoside analogues are effective in the prevention and treatment of hepatitis B exacerbation in kidney transplant recipients, thereby improving patient survival rates. Access to serial HBV DNA monitoring, not only in technical terms but also from a financial point of view, determines how this assay can be best utilized according to local circumstances. When it is not feasible to measure HBV DNA level at frequent intervals, it is not unreasonable to start treatment prophylactically at the time of transplantation, in view of the sinister consequences of delayed therapy. More studies are required to investigate the long-term outcome of patients with drug resistant HBV variants[17-21].

Lamivudine is a safe and effective treatment for hepatitis B reactivation after renal transplantation. Prolonged Lamivudine therapy leads to mutations within the HBV polymerase gene (so-called YMDD variants) that confers resistance to Lamivudine. The development of genotypic resistance increases with duration of therapy (14%, 26%, and 65% after 1, 2, and 4 years). Unfortunately, resistance is accelerated after transplantation (30% after 1 year; 66% after 2 years), due to steroid-enhanced HBV replication[22].

Treatment with Lamivudine in dialyzed patients as well as in kidney-transplanted patients is well tolerated and safe. Effectiveness of Lamivudine therapy in patients undergoing dialysis and in patients with normal renal function is comparable. The YMDD mutation rate in patients undergoing dialysis seems to be low after Lamivudine treatment, while YMDD mutation is frequent in kidney-transplanted patients[23].

Hemodialysis, and renal transplant patients data on antiviral nucleoside analogues are limited (Interferon, Lamivudine and Adefovir).

Nephrotoxicity at the 10 mg dose of Adefovir in patients with normal renal function and compensated liver function has not been observed to date. Gornals et al study showed increased creatinine levels in two decompensated cirrhosis patients and one advanced renal failure patient, all of them receiving immunosuppressive drugs, which could produce synergistic effects with Adefovir[24]. Hence, we believe it is important to monitor the renal function closely in patients receiving concomitant nephrotoxic medications, both of which are common after liver or kidney transplantation[24].

There have been no studies on Telbivudine and Entecavir on chronic hepatitis B with kidney transplant.

Adefovir dipivoxil therapy was safe and effective in chronic hepatitis B patients after kidney transplantation or with renal failure and leads to reductions in serum HBV DNA and ALT normalization similar to that observed in the general population. Lastly, the favorable resistance profile of Adefovir dipivoxil compared with Lamivudine could result

in durability of response which could be an advantage in these medically compromised patients. Fontaine et al demonstrated the efficacy of significant reduction of serum HBV DNA without renal adverse events except the decrease of serum phosphorus, when the doses were adapted to the creatinine clearance[25]. In patients with renal failure, Adefovir dipivoxil is not contraindicated. The dose interval should be adjusted to the creatinine clearance at baseline: 10 mg daily if the clearance is higher or equal than 50 ml/min, 10 mg every 48 hours if it comprised between 50 to 20 ml/minute, 10 mg every 72 hours if it is comprised between 10 and 19 ml/minute and 10 mg once weekly following dialysis in hemodialysis patients, see Table 2.

Table 2: Adefovir Dose in the End Stage Renal Disease

Creatinine Clearance	Dose
>50 ml/min (>0.83 mL/sec/ssa)	10 mg daily
20-50 ml/min (0.33 -0.83 mL/sec/ssa)	10 mg every 48 hr
10-19 ml/min (0.16- 0.31 mL/sec/ssa)	10 mg every 72 hr
<10 ml/min (dialysis patients) (<0.16 mL/sec/ssa)	10 mg once weekly

The dosing interval guidelines were based on a renal pharmacokinetic study in non-HBV infected patients with varying degrees of renal insufficiency. The safety and efficacy of these dosing interval guidelines have not been previously clinically evaluated.

The risk-to-benefit ratio of Adefovir dipivoxil was favorable in patients with renal impairment because there was no significant change in the renal function, except mild hypophosphatemia which could be easily corrected with oral phosphate supplements and an improvement of proteinuria. Biochemical efficacy is difficult to study in that population as patients with renal disease commonly have normal liver transaminases.

Fontaine et al, showed ALT values were normal in 10 patients at the end of the first year of treatment (but 5 of the 12 patients had normal values at the beginning of the treatment, as it is usually reported in post-kidney transplantation patients with chronic hepatitis B)[25]. HBe seroconversion did not occur in Fontaine study of immunosuppressed patients; however, HBeAg seroconversion was reported in the general population at 12% following one year of therapy, increasing to 23% by 72 weeks of therapy. Moreover, a high serum HBV DNA (as frequently observed in immunocompromised patients) is a negative risk factor for HBe seroconversion during Lamivudine therapy. This could suggest a potential lower rate in this population. Virological breakthrough was not observed during the treatment period consistent with the delayed and infrequent incidence of resistance reported in other studies[25-28].

Prevention

Routine vaccination of all patients with end-stage renal disease should rapidly reduce the incidence of HBV infection in dialysis units. Unfortunately, vaccination rates remain low in hemodialysis patients.

It is recommended that an augmented regimen with the vaccine delivered in a four-dose schedule, 40ug per dose given at 0, 1, 2, 6 months, should be administered for patients with end-stage renal disease[29].

Gerald DaRoza prospective cohort study showed that a response to HBV vaccine in patients with CKD, defined by the level of GFR before the start of dialysis therapy[30]. Because strategies with respect to preventative medicine and optimal patient care are being designed for patients with kidney disease regardless of disease severity, these findings have a number of implications, the most important of which is the need for timely identification of patients with kidney disease. Implications for responses to other vaccinations are not known, but may be similar.

However, in Stevens study, it did not show the efficacy of the vaccine in a population of patients receiving dialysis in whom both the rate of antibody response to hepatitis B vaccine and the viral attack rate were low[31]. Other measures to control transmission of hepatitis B virus in dialysis units, including surveillance for hepatitis B surface antigen and isolation of patients who are positive for the antigen, must be continued[31].

It was realized that the immune response of the HBV vaccine was low in the Hemodialysis (HD) patients and it was affected by several factors such as gender, anti-HCV positivity, and nutritional status. It is necessary to isolate the infected patients in separate rooms, their staffs and the expending materials for controlling the HBV infection. In spite of the preventive measures and HBV vaccination, the HBV infection is still a problem in HD units all over the world[32].

If antibody (Ab) titer is greater than 500 IU/L, screening annually is adequate. If the most recent Ab titer is between 100 and 500 IU/L, screening every 6 months is appropriate. If the most recent Ab titer is less than 100 IU/L, screening should be performed every 3 months because the likelihood of losing immunity is greater when Ab titer is low.

Patients with natural immunity should receive a booster dose of vaccine if Ab titer decreases to less than 10 IU/L, as recommended for vaccinated subjects. Patients older than 75 years may be at greater risk for losing immunity and may require closer monitoring. Patients undergoing HD also may benefit from a course of intradermal (ID) vaccination if they fail to respond to intramuscular (IM) immunization or their response is weak[33-35].

Intradermal administration of recombinant HBV vaccine enhances HBV specific B-cell and T-cell responses to recombinant vaccine, which is attributed to high concentrations of dendritic cells and memory T-cells within the dermis. Intradermal administration appears to be more effective than conventional intramuscular vaccination in healthy volunteers. In patients with end-stage renal disease, low dose intradermal vaccination (three to six doses of 5 mg twice per week) achieved protective levels of anti-HBs in more than 90% of both vaccine-naı¨ve and IM vaccine-nonresponders.

Protective anti-HBs responses (10 IU/L) are achieved in only 60% of CAPD patients, 50% of hemodialysis patients, and less than 20% of renal transplant recipients after conventional vaccination schedules. Double-dose regimens and drug combinations with

IL-12 and GM-CSF provide minor additional benefit. GM-CSF enhances the response in the dose and schedule given. Patients who achieved a sero-protective response should be boosted with a 20 μg of recombinant HBV vaccines at the sixth month. Multiple courses of (Granulocyte macrophage colony-stimulating factor) + (recombinant HBV vaccines) administration may improve the rate of response further[35-40].

In addition, intradermal vaccination may also be effective after renal transplantation. Although the durability of anti-HBs response in these studies was superior to intramuscular vaccination, monitoring patients every 6 months is recommended with boosters at one year or when [anti-HBs] falls below 10 IU/L. Intradermal vaccination is well tolerated with only 30% experiencing local discomfort and erythema at the injection site. Future approach in patients with end-stage renal disease may include the new immunogenic recombinant preS1, preS2 vaccines, therapeutic T-cell peptide vaccines, and DNA vaccines[41].

Adoptive immune transfer has been recently discovered as a new approach for inducing immunity to hepatitis B virus (HBV) infection in organ graft recipients.

Transfer of hepatitis B immunity occurs upon the transfer of immunologically active cells from the donor to the recipient by means of an organ graft. Evidence is now presented for the transfer of anti-hepatitis B surface antibodies (anti-HBs) after kidney transplantation in rats. Kidney donors from one syngeneic and two allogeneic rat strains were immunized twice with 4 mg of recombinant hepatitis B vaccine[42].

Potential application of this theoretically useful strategy in clinical kidney transplantation would require the optimization of the peri-operative vaccination protocol regarding dose and timing to ensure potent donor and recipient conditioning[42].

Hepatitis B vaccine is produced by two manufacturers, Merck (Recombivax HB) and GlaxoSmithKline Pharmaceuticals (Engerix-B). Both vaccines are available. Although the antigen content of the vaccines differs, vaccines made by different manufacturers are interchangeable, except for the two-dose schedule for adolescents aged 11–15 years.

The formulations of Recombivax HB are approved for use in any age group. For example, the adult formulation of Recombivax HB may be used in children (0.5 mL) and adolescents (0.5 mL). However, pediatric Engerix-B is approved for use only in children and adolescents younger than 20 years of age. The adult formulation of Engerix-B is not approved for use in infants and children but may be used in both adolescents (11–19 years of age) and adults.

Engerix-B contains aluminum hydroxide as an adjuvant. It does not contain thimerosal as a preservative but contains a trace of thimerosal as residual from the manufacturing process. The vaccine is supplied in single-dose vials and syringes. Recombivax HB contains aluminum hydroxyphosphate sulfate as an adjuvant. None of the formulations of Recombivax HB contains thimerosal or any other preservative. The vaccine is supplied in single-dose vials. Hemodialysis patients should receive 40-mcg dose in a series of three

or four doses. Recombivax HB has a special dialysis patient formulation that contains 40 mcg/mL[43].

Hepatitis B Vaccination Formulations

RECOMBIVAX (Merck)
5 µg/0.5 ml (Pediatric)
10 µg/1 ml (Adult)
40 µg/1 ml (Dialysis)

ENGERIX-B (GSK)
10µg/ 0.5 ml (Pediatric)
20µg/1 ml (Adult)

It has been shown that GeneVac-b, Engerix B, and Shanvac B are highly immunogenic in renal failure and did not show significant differences between each other[44-46].

In hemodialysis patients who had not maintained anti-HBs concentrations of >10 mIU/mL, they have significant HBV infection.

Serologic Testing

Testing after vaccination is recommended for persons (including hemodialysis patients) whose subsequent clinical management depends on knowledge of their immune status. "Testing should be performed 1-2 months after administration of the last dose of the vaccine series by using a method that allows determination of a protective level of anti-HBs (>10 mIU/mL)." "Persons found to have anti-HBs levels of <10 mIU/mL after the primary vaccine series should be revaccinated. Administration of three doses on an appropriate schedule, followed by anti-HBs testing 1-2 months after the third dose, is usually more practical than serologic testing after one or more doses of vaccine." "Persons who do not respond to revaccination should be tested for HBsAg. If the HBsAg test result is positive, the persons should receive appropriate management and any household, sexual, or needle-sharing contacts should be identified and vaccinated. Persons who test negative for HBsAg should be considered susceptible to HBV infection and should be counseled about precautions to prevent HBV infection and the need to obtain HBIG post-exposure prophylaxis for any known or likely parenteral exposure to HBsAg-positive blood."

Booster Doses

"For hemodialysis patients, the need for booster doses should be assessed by annual antibody to hepatitis B surface antigen (anti-HBs) testing. A booster dose should be administered when anti-HBs levels decline to <10 mIU/mL[47].

CONCLUSION

Prevention of nosocomial transmission and treatment of liver disease before renal transplantation should be considered in the management of hepatitis B infection. Finally, vaccination of non-immunized clinical staff and renal patients before the development of advanced renal failure remains the cornerstone of successful management of chronic hepatitis B infection in renal patients.

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