Chapter 2

Treatment of Hepatitis B in Patients With Chronic Kidney Disease

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Abstract

Hepatitis B virus (HBV) is a significant global pathogen, infecting more than 240 million people worldwide. It is a frequent infection in chronic kidney disease (CKD) patients. It negatively impacts long term outcomes reducing graft and patient survival. Current guidelines clearly define who will benefit from antiviral therapy; when to start; what is first-line therapy; how to monitor treatment response; if it may be possible to stop; and how patients should be monitored on therapy. Furthermore, there are some data showing a favourable safety and efficacy profile of nucleos(t)ide analogues in patients with CKD. An important issue for patients with CKD is the risk of life threatening flares of HBV with immunosuppression, either as therapy for their renal disease or following transplantation. The aims of this chapter are to review the epidemiology, risk factors for acquisition and transmission, prognosis, and prevention of HBV infection in individuals with CKD. Thereafter, the treatment options available for HBV infection in individuals with co-morbid CKD, dialysis and renal allografts are discussed.

Key words

Chronic Kidney Disease; Hepatitis B; Treatment
Introduction

Approximately 1.8% of the world’s population are estimated to have been infected by the hepatitis B virus (HBV), which is an important cause of both morbidity and mortality (0.2 deaths/100 person years) worldwide [1]. HBV infection has a complex interplay with chronic kidney disease (CKD) whereby it is able to cause CKD directly through immune related mechanisms, including polyarteritis nodosa and membranous and membranoproliferative glomerulonephritidies, and indirectly by exacerbating metabolic complications including hypertension and diabetes mellitus [2,3]. In addition, CKD portends a poor outcome in individuals with HBV infection, reduces tolerability of HBV therapies, and is itself a risk factor for the acquisition of de novo HBV infection through the need for dialysis, operative procedures, and blood transfusions [1,2]. The aims of this chapter are to review the epidemiology, risk factors for acquisition and transmission, prognosis, and prevention of HBV infection in individuals with CKD. Thereafter, the treatment options available for HBV infection in individuals with comorbid CKD, dialysis and renal allografts are discussed.

Natural History of Hepatitis B Infection

HBV is a blood borne virus that can also be transmitted through exposure to body fluids including sexual exposure and around the time of birth. Exposure to the virus can result in acute hepatitis B, a usually self-limiting disease in immune-competent adults; or progress to chronic HBV infection. Age of exposure has a significant effect on the risk of developing chronic infection as ~40% of infants <2 years old exposed to HBV will develop chronic infection, compared to ~4% if they are ≥2 years old. Immuno-compromise, including from chronic illness, has a similar effect on the risk of developing chronic infection.

Although acute infection occasionally results in life-threatening acute liver failure, most of the morbidity and mortality from HBV occurs with chronic infection. The outcome of chronic HBV infection depends on an interplay of viral, host and environmental factors. For example, in South Africa, chronic HBV and dietary aflatoxin exposure are linked to specific mutations in the p53 tumour-suppressor gene and an aggressive form of hepatocellular carcinoma. The risk of these cancers developing appears increased in individuals with specific isoforms of enzymes involved in aflatoxin metabolism.

In patients with CKD, the major risk of chronic HBV infection relates to liver injury and the development of cirrhosis and related complications. The risk of progressive liver injury in patients with CKD is not just related to the virus. In the immunocompetent host, the hepatitis B virus is not considered cytopathic, that is, it does not appear to directly injure liver cells. Most of the liver injury
is mediated by the immune system attempting to clear infected hepatocytes. This is primarily mediated by T-cells and augmented by innate immune responses. These result in necro-inflammation that stimulates hepatic fibrogenesis and, over time, progression to cirrhosis. The picture is not as clear in immunosuppressed individuals where viral replication occurs at an increased rate and viral proteins can interfere with cellular processes and lead to cell injury and death.

One of the features of chronic HBV infection is that it evolves over time in response to environmental immunological pressures from the host. In an attempt to understand this process, chronic HBV infection is typically depicted as having four phases that reflect the interactions between the immune system and the virus. These are often shown as a continuum (Table 1), implying patients move sequentially through these phases, but in reality an individual’s clinical course can jump forwards or backwards through this sequence and not necessarily encompass all four phases.

These four phases include the immune tolerant phase; hepatitis B e antigen (HBeAg)–positive immune active phase; inactive chronic hepatitis B phase, and the HBeAg-negative immune reactivation phase [4,5]. Phases vary in length from months to decades and while the terminology describing the phases may not accurately reflect the immunological status of the patient in each phase, they are useful for prognosis and guiding the need for therapy [5,6].

Table 1: Natural history of Hepatitis B infection.

<table>
<thead>
<tr>
<th>Phase</th>
<th>ALT</th>
<th>HBV DNA</th>
<th>HBeAg</th>
<th>Liver histology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune tolerant phase</td>
<td>Normal</td>
<td>Elevated, typically &gt;1 million IU/mL</td>
<td>Positive</td>
<td>Minimal inflammation and fibrosis</td>
</tr>
<tr>
<td>HBeAg-positive immune-active phase</td>
<td>Elevated</td>
<td>Elevated &gt;20,000 IU/mL</td>
<td>Positive</td>
<td>Moderate to severe inflammation or fibrosis</td>
</tr>
<tr>
<td>Inactive Chronic Hepatitis B phase</td>
<td>Normal</td>
<td>Low or undetectable &lt;2,000 IU/mL</td>
<td>Negative</td>
<td>Minimal necro-inflammation but viable fibrosis</td>
</tr>
<tr>
<td>HBeAg-negative immune reactivation phase</td>
<td>Elevated</td>
<td>Elevated &gt;2,000 IU/mL</td>
<td>Negative</td>
<td>Moderate-to-severe inflammation or fibrosis</td>
</tr>
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</table>

The immune tolerant phase typically occurs early in chronic infection (often starting in the prenatal period) and is characterised by high HBV DNA and low serum ALT, reflecting a high rate of viral replication and a low inflammatory response. With increasing age, the probability of transitioning to the immune active phase increases. The latter is characterised by both elevated HBV DNA and ALT concentrations reflecting T-cell mediated liver injury. Among individuals in the immune active phase, 70-90% transition to the inactive CHB phase characterised by low or undetectable HBV DNA, normal serum ALT. In some patients, antibody against the HBV e antigen (aHBe) ap-
pears. The final phase is HBeAg-negative immune reactivation phase characterised by elevated ALT and HBV DNA concentrations and absent HBeAg. This picture is typically found late in the infection, with eAg loss due to a combination of immunological pressure and selection for eAg negative mutants. This combination of longstanding disease and immunological pressure against infected hepatocytes means that patients with HBeAg – CHB are more likely to have advanced fibrosis and typically have lower viral loads than those with eAg + disease. This lower viral load means that patients with HBeAg – immune reactivation CHB appear more likely to respond to oral antiviral therapies than those that are HBeAg+.

**Pathophysiology of Hepatitis B Infection**

Our understanding of the molecular mechanisms by which HBV infects hepatocytes and replicates has grown recently; providing new insights into the mechanisms of action of current anti-HBV medication as well as potential novel targets for therapeutic development.

One of the features of the cccDNA is that it is very stable. At present, there is no effective therapy to eradicate HBV cccDNA from infected hepatocytes. Clearance of cccDNA will occur slowly, but only as infected hepatocytes die. This means that antiviral therapies that suppress viral replication are in general only effective as long as they are taken. Once these agents are ceased, the cccDNA provides a template to resume viral replication [7,8].

There are two important feature of the HBV DNAB polymerase. Firstly, it is an attractive therapeutic target as blocking the polymerase effectively blocks viral replication. Secondly, the HBV DNA polymerase has a relatively high rate of making errors during DNA replication. This means that at any time there are likely to be the full spectrum of possible mutations of the virus in circulation. This provides an inherent flexibility in responding to environmental pressure. As an example, the eAg is typically present early in the course of chronic HBV infection. As the immune system increasingly responds to the eAg, there is pressure for the virus to lose the eAg. This typically occurs through specific mutations in the pre-core region of the eAg (the so called pre-core mutant), or a mutation in the basal core promoter; and these changes result in eAg negative chronic HBV infection. This mutagenic potential also allows the development of resistance to antiviral agents [7,8].

**Epidemiology**

Hepatitis B affects approximately 350 million people worldwide and is associated with high mortality and morbidity [9,10]. Deaths from cirrhosis and hepatocellular carcinoma were estimated at 310,000 and 340,000 per
year, respectively [1].

Apart from major liver complications, clinical evidence suggests that chronic HBV infection has a negative impact on renal function [11]. HBV infection can lead to glomerulonephritis, even in the absence of cirrhosis [12]. A small controlled prospective study indicated that individual estimated glomerular filtration rate declined by approximately 2mL/min/year in 60 untreated HBV-infected patients without pre-existing renal disease, diabetes or hypertension during the median follow-up of 24 months [13]. A two-year cross sectional Hepatitis and Renal Parameters Evaluation (HARPE) study observed that 64.6% of treatment-naive patients with chronic HBV infection had evidence of CKD [14]. A two year GLOBE study indicated that telbivudine, one of the agents that inhibits DNA replication, improved renal function in patients with chronic HBV infection [15].

Over the past few decades, there has been a substantial decrease in the incidence of HBV infection in haemodialysis patients, probably attributable to screening of blood donors, a decline in blood transfusion requirements with increased erythropoietin use, and authoritative guidelines relating to infection control and vaccination [16]. Despite this progress, haemodialysis patients remain at increased risk of acquiring HBV because of increased exposure to blood products, shared haemodialysis equipment, frequent breaching of skin, immunodeficiency, and continuing high prevalence rates of HBV infection among haemodialysis populations [17]. Although acute infection tends to be mild and asymptomatic in dialysis patients, up to two-thirds may progress to chronic carriage, with significant risk of chronic liver disease, premature death from cirrhosis or liver cancer and nosocomial transmission within haemodialysis units [17].

**Hepatitis B Infection as a Risk Factor for Chronic Kidney Disease**

HBV can cause CKD directly through immunological mechanisms or indirectly through metabolic complications. HBV has been implicated in the genesis of polyarteritis nodosa, membranous glomerulonephritis and membranoproliferative glomerulonephritis [2,9,18]. The pathogenic role of HBV in these processes is secondary to the formation of hepatitis B antigen-antibody complexes and their deposition in the medium sized arteries and glomeruli.

In polyarteritis nodosa, a medium-sized vessel vasculitis, antibody-antigen complexes are deposited in vessel walls [9]. In membranous nephropathy, it has been proposed that deposition of HBeAg and anti-HBe antibody forms the classic subepithelial immune deposits [2]. Both HBsAg and HBeAg have been implicated in membranoproliferative glomerulonephritis, which has been characterised by deposits of circulating antigen-antibody complexes.
complexes. In addition, hepatitis B is a risk factor for the development of hypertension and diabetes mellitus, which are present among 6% and 9% of patients with hepatitis B, respectively [18]. These metabolic complications are established risk factors for the development of CKD.

**Impact of Chronic Kidney Disease on Hepatitis B**

Renal parameters are of utmost importance in CHB patients since renal dysfunction impacts clinical outcomes. In a prospective study including patients with HBV infection, an elevated serum creatinine at baseline was significantly associated with mortality rates at 6 months in multivariate analysis, with a hazard ratio (HR) for death of 5.23 [17]. Additionally, it has been shown that HBV infection increases the risk of occurrence of kidney disease in Chinese diabetic patients [17]. Furthermore, therapeutic management of HBV infection is potentially modified in the presence of CKD, while antiviral drugs dosages must be adjusted to renal function and potential renal toxicity of antivirals may further damage the kidneys and lead to clinical complications [17].

**Diagnosis of Hepatitis B Infection**

The diagnosis of hepatitis B relies on serological testing. There are five routine tests used that, in combination with HBV DNA testing, provide a guide to the stage of infection. The antibody to HBV core antigen (aHBc) provides evidence that an individual has been exposed to the HBV virus. (The HBV core antigen itself is not found in peripheral blood, but is present on hepatocytes). If a patient is aHBc IgM positive, then this exposure was within the last 6 months. On the other hand, if aHBc IgG is present, it is taken as evidence that the HBV exposure was >6 months ago [19].

The HBV surface antigen (HBsAg) is a marker of current infection, and in combination with aHBc IgM indicates this is an acute infection; or with aHBc IgG, a chronic infection. The antibody to HBsAg (aHBs) is a neutralizing antibody that blocks infection. If a patient has aHBs then they are immune to HBV or have resolved infection [20].

The remaining two serological tests are the HBV e antigen and the antibody to this antigen (HBeAg and aHBe respectively). In chronic infection, these tests are useful to distinguish the stage of disease, as discussed above. The other essential HBV test is HBV DNA testing. The viral load in particular is useful in determining the need for antiviral therapy. If the viral load is low, then oral antiviral therapy is unlikely to add further benefit in suppressing necro-inflammation. However, in chronic hepatitis B, a high HBV DNA in the presence of advanced liver disease or raised liver enzymes indicates there may be a benefit from viral suppression. Viral load testing is also used to monitor response to therapy, and typically should fall over three to six months after commencing oral agents [20].
Other tests that are available include HBV DNA sequencing for mutations, and HBV genotyping. DNA sequencing is generally used to look for mutations that confer resistance to oral antiviral agents, but is occasionally used to look for other clinically relevant mutations. Resistance testing is particularly useful in determining whether apparent failure of oral agents may be due to non-compliance, or the emergence of specific mutations, in which case the results may be used to guide changes to therapy. Genotyping is variably used in clinical practice, but does provide information on risk of disease progression and potential for response to different antiviral therapies [19,20].

Finally, there are imaging and other modalities, such as ultrasound, liver biopsy, fibroscan and serological tests for hepatic fibrosis that are used to determine the stage of disease; whether cirrhosis is present; and to look for complications of chronic hepatitis B infection, such as portal hypertension and hepatocellular carcinoma [19,20].

**Therapy**

**Current Therapies of Hepatitis B**

Seven drugs have received approval for the treatment of chronic HBV infection, including interferon-α, PE-Gylated interferon-α, the nucleoside analogues lamivudine, telbivudine and entecavir, and the nucleotide analogues, adefovir and tenofovir, referred to as a group as NAs.

The NAs as a group share a number of characteristics. They all act to inhibit the HBV DNA polymerase by sitting in the enzymatic pocket of the enzyme and blocking DNA chain elongation. Mutations of the HBV DNA polymerase that change the configuration of the pocket may block the entry of a specific agent and confer resistance to the agent. With the first generation agent lamivudine, this could occur with one mutation. However for later agents, such as entecavir and tenofovir, multiple mutations are required to confer resistance. This need for multiple mutations is said to confer “a high genetic barrier to resistance”, and means that it is unlikely to occur spontaneously. There is cross reaction in terms of the development of resistance, so that the development of resistance to lamivudine makes it more likely that resistance will occur with telbivudine and entecavir. However, the configuration of adefovir/tenofovir are such that lamivudine resistance does not appear to confer a major increase in the risk of resistance developing for these agents. Another factor that can contribute to the development of resistance is inadequate initial response or poor compliance. Resistance can develop in these settings because the inherent mutagenic potential of the DNA polymerase will allow the eventual emergence resistant species unless viral replication is fully suppressed.

In terms of potency, entecavir, telbivudine, and tenofovir are the most potent, followed by lamivudine and then adefovir. Entecavir and tenofovir are associated with the lowest risk of drug resistance, followed by adefovir, tel-
bivudine, and lamivudine, in that order [9].

**Interferon-α**

Interferon-α, an antiproliferative and immunomodulatory agent, was the first available antiviral drug for chronic HBV infection. This agent is metabolized by renal tubules. In dialysis patients, it has been found that interferon-α’s half-life is greatly enhanced, and prolonged treatment can lead to drug accumulation; hence, its adverse effects are magnified. The most problematic of these are neuropsychiatric side effects (including irritability, impaired concentration and depression), leucopenia and thrombocytopenia; but also include flu-like symptoms, nausea, diarrhea, fatigue, thyroid dysfunction, and alopecia [21]. Therefore, interferon-α is poorly tolerated by dialysis patients who have a frequent occurrence of side-effects, such as exacerbation of anaemia, neutropenia, and protein malnutrition. Scarce data exist on treatment with interferon-α among infected dialysis patients with HBV. In one study, the adverse effects were so severe that withdrawal of the drug was required in more than 50% of patients [22]. Newer PEGylated interferon, an agent with a longer half-life, is no better tolerated in patients with renal failure. Interferons are not recommended in dialysis patients with HBV infection.

**Lamivudine**

Lamivudine was the first nucleoside analogue antiviral approved worldwide for the treatment of chronic hepatitis B. Its major advantages include ease of administration (oral), potent antiviral activity, and favourable safety profile. Lamivudine has also been shown to be effective in the treatment of HBV-associated, acute glomerulonephritis [23]. Good results were obtained in a series of 16 dialysis patients: 56% were able to eliminate HBV DNA and 36% were able to clear HbeAg [24]. The main disadvantages of lamivudine include risk for drug resistance and the need for usually indefinite treatment. Lamivudine-resistant HBV developed in 39% of dialysis patients after a median of 16.5 months of treatment [25]. The prevalence of drug resistance increases with the duration of the therapy, and is present in 14% of patients treated for one year, and in 69% of patients after 5 years of antiviral therapy [22]. The development of drug-resistance is a major limitation to its long term use [20,25]. Another potential issue is the need for dose adjustment in renal impairment.

**Adefovir dipivoxil**

Adefovir dipivoxil, a nucleotide analogue, is the second oral agent approved for the treatment of chronic HBV infection. It has generally been used as additive therapy for lamivudine-resistant CHB [26] because lamivudine resistance does not impact on adefovir efficacy or the risk of adefovir resistance [27,28]. Resistance is less of an issue
than with lamivudine; 0% at one year and 29% at 5 years [29]. One limitation to its use in CKD is that adefovir is a nephrotoxic agent [22], and worsened renal function has been reported in 2.5 to 28.0% of cases after 1 to 2 years of therapy [22]. Limited data about adefovir administration exist in the chronic kidney disease population [30,31]. Adefovir is eliminated via the kidneys; thus, a dose adjustment is required in CKD patients to prevent drug accumulation and toxicities [27].

**Telbivudine**

Telbivudine is a synthetic thymidine nucleoside analogue that inhibits HBV DNA polymerase [32], and provides effective and sustained viral suppression [33]. In clinical trials, telbivudine has been superior to lamivudine in HBV patients in terms of treatment outcomes and HBV DNA suppression [33,34]. When compared with lamivudine, telbivudine has greater HBVDNA suppression, and HBeAg seroconversion rates are significantly greater with telbivudine than with lamivudine [35]. In addition, telbivudine-treated subjects are less likely to develop viral resistance than lamivudine-treated individuals [33,36]. Nonetheless, rates of resistance developing were still higher than with the more potent agents, Tenofovir and entecavir and this has limited the uptake of telbivudine therapy.

**Entecavir**

Entecavir is a nucleoside analogue drug that has selective anti-HBV activity. The incidence of entecavir resistance appears to be minimal, only about 1% after 3 years of monotherapy [37]. Entecavir is effective in viral suppression [38,39]. In addition, entecavir is more potent at suppressing HBV replication than lamivudine and adefovir [21]. Although there is little information on the therapeutic impact of entecavir in dialysis patients with chronic HBV infection, it is often recommended as a first-line oral therapy in patients with kidney disease [21]. Because entecavir is primarily eliminated by the kidneys, dosed reduction is recommended for patients with reduced GFR [40]. Moreover, the drug should be administered after haemodialysis. Continuous ambulatory peritoneal dialysis can remove approximately 0.3% of the dose over 7 days. Entecavir should be administered on an empty stomach (at least 2 hours after a meal or 2 hours before the next meal).

**Tenofovir**

The nucleotide analogue tenofovir is the other agent recommended as a first-line oral antiviral in the treatment of chronic HBV patients with normal renal function [19]. It is the most potent agent against HBV infection within the first year of treatment [41]. Tenofovir can also be an effective alternative in patients with lamivudine-resistant HBV infection and is more potent and efficacious than adefovir [42]. However, nephrotoxicity and acute kidney
injury have been reported in some patients treated with tenofovir [43,47]; therefore, the drug should be used with care in dialysis patients with residual renal function.

**Impact of Antiviral Agents on Renal Function**

Nucleoside and nucleotide analogues are primarily eliminated without changes in the urine following ingestion, and appropriate dose modifications are recommended for patients with impaired renal function (GFR < 50 mL/min). Treatment guidelines recommend that all patients initiating NA treatment should be tested for serum creatinine levels and estimated creatinine clearance before therapy; and baseline renal risk should be assessed for all of them [19,48]. High baseline renal risk includes one or more of the following clinical situations: decompensated cirrhosis, creatinine clearance < 60 mL/min, poorly controlled hypertension, proteinuria, uncontrolled diabetes, active glomerulonephritis, concomitant nephrotoxic medications and solid organ transplantation. In consequence, dialysis recipients may have many of these basal renal risk factors. In clinical trials outside renal transplant setting, minimal decline in renal function has been shown with all NAs, except for telbivudine which appears to improve renal function [49,50].

First line NAs, entecavir and tenofovir, appear to have little impact on renal function in the general population when compared with untreated controls and with the other NAs. Although there is some evidence of renal dysfunction in entecavir-treated patients, its clinical significance remains unclear as it may represent a physiological decrease in renal function in this group and/or reflect the potential limitations of standard biochemical tests of renal function in patients with liver disease [51]. Baseline renal risk factors may play a role in the nephrotoxic effects of NAs. Therefore, it is recommended that patients going on these agents should have baseline measures of serum creatinine and estimated creatinine clearance. For adenovirus- or tenofovir-treated patients, it is also advised to measure serum phosphate levels, especially in patients at high renal risk. In patients at low renal risk, these tests can be performed every 3 months during the first year and every 6 months thereafter, if there are no renal adverse events. In patients at high renal risk these tests can be performed every month for the first 3 months, every 3 months until the end of the first year and every 6 months thereafter, if there are no renal adverse events. Closer renal monitoring is required in patients who develop reductions in creatinine clearance < 60 mL/min or reductions in serum phosphate levels < 2 mg/dL (0.65 mmol/L) [19,48,52,53].

**HBV Vaccination**

HBV vaccination represents one of the most important measures in the prevention of nosocomial transmission of HBV infection within a dialysis unit, especially in endemic areas. Unfortunately, despite the high seroconversion rate of more 95% in general population, the seroconversion rate obtained using current HBV vaccination
strategies in dialysis patients remains relatively low. With conventional intramuscular (i.m.) vaccination, only 50-73% of dialysis patients develop protective levels of anti-hepatitis B surface antibodies (aHBs) [54,55]. In addition, the antibody response in patients with end-stage renal disease (ESRD) tends to be short-lived, with 23-57% of initial responders having undetectable aHBs within 6-12 months [56,57]. Various strategies have been developed to improve the response rate to HBV vaccination in dialysis patients. These include increasing the dose and frequency of vaccination, using an alternative route of administration, use of adjuvants and the development of novel immunogenic vaccines [58-61]. There are only a few studies of the last two strategies and the results remain preliminary and inconclusive. However, there are many studies on changing the dose, frequency and route of vaccine administration and it is recommended that an augmented regimen be employed for patients with end-stage renal disease with the vaccine administered in a four-dose schedule, 40 µg per dose given at 0, 1, 2, 6 months, instead of the conventional 3-dose schedule of 20 µg per dose given at 0, 1, 6 months [55]. Nevertheless, the superiority of this regimen has not yet been confirmed [61,62]. There are also studies on intradermal (i.d.) administration of the vaccine. It has been suggested that by activating epidermal Langerhans cells and keeping the antigen in the tissue for longer time, intradermal administration might reverse the dysfunctional antigen presentation associated with uraemia and enhance T and B lymphocytes responses. To date, the results of these studies have been mixed and the efficacy of intradermal hepatitis B vaccination remains controversial [63-65]. From these studies, it seems that the efficacy of i.d. vaccination is dose-related and superior efficacy probably could only be achieved with high individual and cumulative doses. For example, by using an individual dose of 5.0 µg and a mean cumulative dose 40-57.3 µg, i.d. administration was no better than i.m. vaccination. Another study on dialysis patients comparing 20 µg i.d. with 40 µg i.m., both given for three doses, also showed no difference in the aHBs seroconversion rate [66]. In contrast, with an individual dose of 20 µg and cumulative dose of 100 µg, Propst et al. [67] showed that i.d. vaccination was superior to i.m. administration with four dose-dose schedule (40 µg/dose) in terms of the seroconversion rate (94 vs. 76%). However, the induced immunity by i.d vaccination is less durable than conventional i.m. administration. Although it is considered unnecessary to maintain an anti-HBs greater than 10 mIU/mL for low-risk healthy population after successful vaccination and initial seroconversion because of the presence of immunologic memory, a booster dose of vaccine is generally recommended for dialysis patients due to their immunosuppressive state, poor responses to vaccination and environmental risks of cross infection [55]. In this regard, the limited durability of i.d vaccination would be another important consideration and concern before routine application in daily practice. With a recent study showing that in patients with chronic
kidney disease, the higher the glomerular filtration rate; the better the response to HBV vaccination [68], it would be highly recommended to consider vaccinating all HBV non-immune patients once they are diagnosed as having renal disease or implementing universal vaccination in endemic areas.

Dialysis Patients

Prevention of HBV transmission is a key consideration in the care of patients receiving haemodialysis. The introduction of HBV immunization has significantly lowered the HBV incidence in several endemic regions, although CKD patients often have poor responses to vaccination as detailed above [69,70]. It should also be noted that haemodialysis patients with chronic HBV infection often present with moderate or no elevations of serum aminotransferases owing to altered inflammatory response, lower serum HBV DNA levels due to its removal by haemodialysis, higher risk of occult HBV infection (usually aHBC-positive, HBsAg-negative, aHBs-negative), and many comorbidities such as cardiovascular disease, diabetes mellitus, and anemia [71-73]. All of these parameters may affect the clinical and laboratory presentation and course of chronic HBV infection and the patients’ response to antiviral therapy.

The optimal therapy for chronic HBV infection in patients on haemodialysis depends on the clinical picture. If patients have advanced liver disease or chronic HBV with raised liver enzymes and high DNA, they should be treated. The difficulty is what to do with those who do not have these biochemical parameters. If the HBV DNA concentration is high but the ALT is normal, observation with regular fibroscan monitoring is recommended [72]. A limited literature exists on IFN therapy on patients with chronic HBV infection receiving haemodialysis. The experience in this patient group comes mostly from treatment of hepatitis C [72]. Although IFN-α administration can lead to HBe seroconversion and improvement of liver biochemistry, IFN side effects (mostly myelosuppression and malnutrition) hamper its use in clinical practice.

There are limited data on NA therapies in haemodialysis patients that suggest they are safe and potent antivirals. There are three reports including five HBV patients undergoing haemodialysis who were treated with adefovir for 12–30 months [73]. Both liver and renal function improved in parallel with the serum HBV DNA clearance. There are no data for telbivudine efficacy or safety in such patients [73,74]. Long-term entecavir therapy seemed to be safe and effective in nine patients on maintenance haemodialysis. Given its high potency and high genetic barrier in NA-naive patients profile, entecavir is the most promising anti-HBV agent for patients undergoing haemodialysis and/or candidates for renal transplantation [69,70]. As long-term entecavir therapy is not recommended in patients with lamivudine resistance, tenofovir may be required in such cases, although caution should
be exercised and doses should be appropriately adjusted in patients with estimated glomerular filtration rates <50 ml/min [72-75].

Transplant Patients

Candidates for Renal Transplantation

HBsAg-positive patients with cirrhosis and end-stage renal disease are at risk for hepatic decompensation after isolated renal transplantation, and may require consideration for simultaneous liver and kidney transplantation [99,76,77]. According to the current guidelines, all HBsAg-positive candidates for solid-organ transplantation should be treated with NAs before renal transplantation in order to maintain undetectable HBV DNA, reduce liver fibrosis, and prevent hepatic decompensation after renal transplantation [78]. In clinical practice, the optimal timing for treatment initiation in HBsAg-positive candidates for renal transplantation is often individualized, taking into account the recipient's clinical status, dialysis-related complications, and, most importantly, the expected waiting time on hemodialysis [77,78].

HBV-Positive Renal Transplant Recipients

IFN-α therapy is contraindicated in renal transplant recipients owing to the increased risk of acute rejection and low antiviral potency. In 2009, KDIGO recommended prophylaxis with entecavir, tenofovir, or lamivudine for HBsAg-positive transplant recipients [79]. The application of NAs prompted a new era in renal transplantation of HBV-positive transplant recipients. Before their use, HBsAg positivity was an independent and significant risk factor for mortality and graft loss [79]. The effective NA therapy permitted a striking increase in patient (81–89%) and graft survival (86%) at 10 years, through the inhibition of viral replication, the retardation of liver disease progression, and the lower incidence of hepatocellular carcinoma (the cancer risk is not eliminated, and ongoing HCC surveillance is recommended) [80].

The pre-emptive use of NA therapy is recommended to all HBsAg-positive patients shortly before or at the time of renal transplantation regardless of the baseline histological severity and serum HBV DNA level, because immunosuppressive therapy after renal transplantation has been associated with a risk of rapidly progressing fibrosing cholestatic hepatitis even in patients with mild or inactive liver disease before renal transplantation [80]. Salvage NA therapy after post-renal transplantation HBV exacerbation can be used, but it is a less effective approach compared with pre-emptive NA therapy and confers excessive risk to patients. Treatment with a NA should usually continue for as long as immunosuppressive therapy lasts or at least for 24 months if immunosuppression is withdrawn before then. The need for HBV therapy in HBsAg-negative, anti-HBc-positive transplant recipients is debatable. If the decision is made not to place this group on prophylactic therapy, then ongoing monitoring is necessary to
detect HBV reactivation early prior to potentially serious flares in HBV.

In non-renal patients, including those who undergo liver transplantation, monotherapy with a NA with high genetic barrier (entecavir or tenofovir) is currently recommended [81]. Although there are very limited data in transplant recipients, entecavir is often considered as a preferable initial option in this setting because of the theoretical lower risk of nephrotoxicity compared with tenofovir. Data for entecavir have included a total of 80 NA-naive or lamivudine- or adefovir-resistant HBV transplant recipients with satisfactory results [81]. Entecavir given at a daily dose of 1 mg for a maximum of 33 months was found to be effective, well tolerated, and without deterioration of renal function, microalbuminuria, or allograft rejection [81,82]. Data for tenofovir have been reported for only three HBV transplant recipients. Tenofovir given at a dose of 245 mg adapted according to renal function was found to be effective, well tolerated, and safe without changes in serum creatinine levels after 12 months of therapy [82].

**HBV-Positive Renal Transplant Donors**

Kidneys from HBsAg-positive donors are not promoted for renal transplantation, because they have the potential to transmit HBV to the recipient [83]. Nevertheless, the fundamental need for donor pool expansion urged some transplant centres to use kidneys from HBs-Ag positive, or anti HBC-positive/ HBsAg negative donors to HBsAg-positive and -negative transplant recipients [83,84]. Indeed, there are reports for safe and effective lamivudine prophylaxis in HBsAg-negative transplant recipients of kidney grafts from anti-HBc-positive donors and for lamivudine combined with immunoglobulin in anti-HBs-positive recipients having received grafts from HBsAg-positive donors (with or without detectable HBV DNA) [84-86].

**Immunosuppression in Patients with Renal Disease**

Patients with chronic renal failure are at high-risk for infectious complications, similar to patients with other types of acquired immune defects or those on immunosuppressive therapy. Secondary immune failure in uraemia is multi-faceted and is influenced by uraemic intoxication per se, by altered renal metabolism of immunologically active proteins and by specific effects of renal replacement therapy. Large inter-individual variability points to the importance of individual factors. A high incidence of infection is found in uraemic patients and infections remain the second most frequent cause of death.

One specific problem is hepatitis B. Vaccination against hepatitis B is routinely performed in dialysis patients. Although effective in only 60–70% of patients, it helped to eliminate the threat of hepatitis B from dialysis centres. The response to hepatitis B vaccine proved to be
a valid clinical index for individual immune reactivity in dialysis patients.

Rituximab has been used in a variety of renal diseases and in renal transplantation, with anecdotal success. It is an engineered chimeric monoclonal antibody that contains murine heavy and light chain variable regions directed against CD20 plus a human IgG1 constant region. The CD20 antigen, a transmembrane protein, is found on immature and mature B cells, as well as on malignant B cells; this antigen is found in more than 85% of non-Hodgkin's lymphoma. CD20 mediates B-cell proliferation and differentiation. The CD20 antigen is not internalized upon antibody binding, and is not shed or found in soluble forms. Following treatment with rituximab, B cells are prevented from proliferating, and undergo apoptosis and lysis through complement-dependent and complement-independent mechanisms. These mechanisms include complement-dependent cytotoxicity, antibody-dependent cell cytotoxicity, and activation of tyrosine kinases as a direct effect of the antibody binding to its CD20 ligand. The exact contribution that each of these mechanisms makes in vivo remains unclear. Evidence that the degree of B-cell depletion correlates with levels of serum rituximab and the Fcgr3a genotype indicates that antibody-dependent cell cytotoxicity is crucial; however, prolonging the ‘off rate’ of the monoclonal antibody seems to increase complement-dependent cytotoxicity and therapeutic efficacy, indicating that complement-dependent mechanisms are also important. B-cell depletion generally persists for 6–9 months in over 80% of patients, although the degree of depletion is highly variable. The concerns regarding using rituximab in patients with CKD is the activation of Hepatitis B. Screening for prior exposure to Hepatitis B is crucial when considering the commencement of rituximab in CKD patients.

Prevention of Transmission of Hepatitis B within Dialysis Units

Infection control precautions for dialysis services are more stringent than standard precautions and are designed to prevent transmission of blood borne viruses and bacterial pathogens including Multi-Resistant Organisms (MRO), in dialysis settings. They include all the components of standard precautions as well as routine serological testing, hepatitis B vaccination, surveillance for infections, additional cleaning procedures and the management of equipment, medications and consumables.

To prevent the transmission of HBV, dialysis services should institute a comprehensive blood borne virus prevention plan, including a high level of compliance with BBV serological testing and HBV vaccination. The criteria for separating HBsAg reactive patients undergoing peritoneal dialysis should be the same as those undergoing haemodialysis since peritoneal fluid can contain high levels of HBV and should managed in the same manner as the
patient’s blood.

The following approach to management of patients infected with HBV is recommended. The measures are ranked from the most to least preferred method for managing HBV-positive patients, and should be adopted based on the number of adequately trained staff, the availability of isolation facilities, and the ability to ensure patient and staff safety:

- **Dialyse HBV-positive patients in a separate room/area designated only for HBV-positive patients. This should include the use of separate dialysis equipment including machines.**

- **Patients with HBV should be managed separately from other patients.**

- **If there are no isolation facilities, HBV-positive patients should be separated from susceptible patients and undergo dialysis on dedicated machines.**

- **Patients with aHBs greater than 10 IU/L may undergo dialysis in the same area as HBsAg-reactive patients, or they may serve as a geographic buffer between HBsAg-reactive and susceptible patients (non reactive for HBsAg, aHBs, aHBc).**

- **When HBV-positive patients are not being dialysed, the room/area may be used for uninfected patients after cleaning and disinfection.**

- **Machines, equipment and consumables should be managed appropriately.**

  - Ideally, the same dialysis equipment should not be used for the HBV-positive patients and seronegative patients; however, where this is not possible, the machine should be disinfected using conventional processes and the external surfaces cleaned and disinfected thoroughly prior to use on another patient.

  - When a machine is no longer required for HBV-positive patients, it can be returned to general use after standard cleaning and disinfection procedures have been carried out.

- **Dialysis staff members caring for HBV-positive patients should not care for susceptible patients at the same time (e.g. during the same shift or during patient change-over).**

- **Staff members can care for HBsAg-reactive and patients with aHBs titre greater than 10 IU/L during the same shift.**

- **If dialysis staff members must care for both HBV-positive patients and susceptible patients during the same shift, they must meticulously adhere to Standard Precautions i.e. change their apron, gown and gloves, and perform hand hygiene between patients.**
Conclusion

The primary effort for HBV eradication and thus reduction of HBV-associated kidney disease is based on global HBV immunisation and appropriate screening programs. NAs with high genetic barrier to HBV resistance are the best options for HBV-positive patients with CKD in order to minimise the consequences of HBV infection. Combination with immunosuppressive agents may be considered in cases of rapid renal function deterioration and/or severe proteinuria. All HBsAg-positive candidates should be treated with NAs before renal transplantation in order to maintain undetectable HBV DNA, reduce liver fibrosis, and prevent hepatic decompensation after renal transplantation. Ultimately, large multicenter controlled studies are required to evaluate the therapeutic benefits, the long-term safety and the optimal regimen of NAs for different groups of chronic HBV patients with CKD.

References


22. Wong PN, Fung TT, Mak SK, Lo KY, Tong GM. Hepatitis B virus infection in dialysis patients. J


34. Lai CL, Gane E, Liaw YF, Hsu CW, Thongsawat S. Telbivudine versus lamivudine in patients with


41. Woo G, Tomlinson G, Nishikawa Y, Kowgier M, Sherman M. Tenofovir and entecavir are the most effective antiviral agents for chronic hepatitis B: a systematic review and Bayesian meta-analyses. Gastroenterology. 2010; 139: 1218-1229.


57. Fleming SJ, Moran DM, Cooksley WG, Faoagali JL. Poor response to a recombinant hepatitis B


67. T Propst, A Propst, K Lhotta, W Vogel, P König. Reinforced intradermal hepatitis B vaccination in hemodialysis patients is superior in antibody response to intramuscular or subcutaneous vaccin-


78. Park KS, Han DJ, Park JB, Park JS, Park S. Long-term outcome of Hepatitis B-positive renal al-


