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Hepatitis B virus infection: implications in chronic kidney disease, dialysis and transplantation

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Summary

Hepatitis B virus (HBV) infection occurs worldwide but is most prevalent in Southeast Asia and sub-Saharan Africa with reported prevalence rates varying from 3 – 26 %. The higher prevalence of infection has been reported in patients with HBV and human immunodeficiency virus (HIV) co-infection. Hepatitis B virus not only affects the liver but has also been implicated in the pathogenesis of membranous, membranoproliferative and mesangial proliferative glomerulonephritides. Though controlling the spread of HBV infection in renal dialysis units has been one of the major triumphs in the management of end-stage renal disease, transmission of HBV can still occur through contamination of equipments and environmental surfaces and the use of multiple dose vials of drugs. Some reports have indicated that prior HBV infections have negative impact on graft and host survival following transplantation. Interferon can be used in the treatment of HBV-associated glomerulonephritides (HBV- GN) but is contraindicated in transplantation because of its immuno-modulatory effects. Despite the fact that patients with chronic kidney disease (CKD) have suboptimal response to HBV immunization, immunization is still beneficial to these patients. However, reports indicate that most patients with CKD were either not immunized or were given suboptimal doses. Control of HBV in the population by immunization can lead to a reduction in the prevalence of HBV- GN. In addition, immunization of patients with CKD will help in controlling HBV infection in dialysis settings and can lead to improved graft and host survival following transplantation.

Keywords: *Hepatitis B infection; chronic kidney disease, dialysis, transplantation*

Résumé

L'infection du virus de l'hépatite B (HBN) apparaît dans le monde entier mais plus prévalent en Asie du Sud Est et en Afrique Sud du Sahara avec un taux variant entre 3-26%.Le taux élevé de prévalence de l'infection a été reporté chez les patients ayant la co-infection du HBV et le virus immunodéficitaire acquis (HIV). Le virus non seulement affecté le foi mais aussi la pathogènese des membranes, la prolifération des membranes et la prolifération des glomérulaires mesagiale. Bienque contrôle l'infection du HBV dans les unités de dialyse rénale a été l'un des triomphe important du ménagement de l'etat final des maladies rénales, la transmission du HBV peut être par la contamination des équipements et les surfaces environnementales et l'usage des multiples régiment thérapeutiques. Certains rapports ont indiques que l'infection du HBV ont des impact négative sur le greffage et la survie de l'individu post-transplantation. L'interféron peut être utilise pur le traitement du HBV associé aux glomerulonephritites (HBV-GN) mais contra indique a la transplantation a cause de effets des immunomodulateurs.Bienque certains patients ayant une chute rénale chronique(CKD) ont des réponses sous optimales aux immunisation au HBV , l'immunisation reste bénéfique aux patients. Le contrôle du HBV dans la population par l'immunisation peut réduire la prévalence du HBV-GN. En plus l'immunisation des patients avec CKD aidera a contrôle les infection du HBV en lieux de dialyse et pourrait améliorer le greffage et la survie après la transplantation.

Introduction

Following the discovery of the hepatitis B surface antigen (HBsAg) by Blumberg *et al* [1] it became apparent that HBV infection is widespread in man. Worldwide, approximately 350 million people are chronic carriers with the majority in Asia and sub-Saharan Africa [2,3]. It is estimated that every year more than 50 million people are infected with HBV and more than two billion individuals have already been infected [2]. Hepatitis B virus (HBV) causes about 2 million deaths worldwide per year from liver affectation alone [4].

Epidemiology of hepatitis B virus infection

The prevalence of HBV varies from 0.1 % to 2 % in low prevalence areas (United States, Canada, Western Europe) to 3 % to 5 % in intermediate prevalence areas (Mediterranean countries, Japan, Central Asia, Middle East, South America) to 10 % to 20 % in high prevalence areas (Southeast Asia, Sub-Saharan Africa) [5].

In Nigeria, there is a dearth of population-based studies on HBV carrier rate as determined by the prevalence of hepatitis B surface antigen (HBsAg), though many hospital-based studies abound. Olumide in a population study of healthy adults in Ibadan reported a prevalence rate of 12.6% [6]. The prevalence rate of HBsAg in blood

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donors in Nigeria varies between 6 – 11 % [7,8]. Fakunle *et al* in Zaria reported a prevalence rate of HBsAg 45.9 % in children under 10 years and 10 % in adults over 30 years [9]. Gashau *et al* in Maiduguri reported a prevalence of 36.2 % in a hospital-based study [10]. Ojule *et al* [11] and Harry *et al* [12] reported a prevalence of 4.3 % and 11.6 % in pregnant women in Port Harcourt and Maiduguri respectively. A prevalence rate of 18.3 % was reported in patients requiring dental extraction in Ibadan with a higher infection rate in men compared to women (23.1 % vs. 14 %) [13]. With the advent of human immunodeficiency virus (HIV)/ acquired immunodeficiency syndrome (AIDS), a higher prevalence rate of HBV infection has been documented in patients living with HIV / AIDS [14,15]. Uneke *et al* [14] in Jos found that 25.9 % of HIV-infected individuals were HBsAg seropositive compared with 14.3 % in blood donors. Among the HIV – infected patients, males had consistently higher HBsAg seroprevalence compared to females (31.8 vs. 22.1 %). Reports from other parts of Africa showed a carrier rate of 4.4 % in Tanzania [16] 14.8 % and 17 % amongst blood donors and rural adult males in Namibia respectively [17].

Structure, serological diagnosis and modes of transmission of hepatitis B virus

Hepatitis B virus is a deoxyribonucleic acid (DNA) virus belonging to the family of hepadnaviruses. The complete virus is 42 nm in diameter and consists of an envelope and the nucleocapsid core [18,19]. The envelope is composed of viral-encoded proteins and host-derived lipid components. The nucleocapsid core contains the viral genome and a relaxed-circular partially duplex DNA of 3.2 kb and a polymerase that is responsible for the synthesis of viral DNA in infected cells. HBV can also exist as 22nm subviral filaments and spheres that are composed of only envelope glycoproteins and host-derived lipids and typically outnumber virions by 1000:1 to 10,000:1 [19].

The HBV genome has four long open reading frames (ORFs). The preS-S (presurface-surface) ORF encodes the three envelope glycoproteins known as the large (L), middle (M) and small (S) HBsAg. The L protein is thought to play key roles in the binding of the virus to host cell receptors and in the assembly of the virion and its release from the cell. The function of the M protein is unknown. It has been suggested that a domain within the S protein may be involved in the attachment to the hepatocytes also, bringing the viral particle into close contact with the cell membrane and thus facilitating the specific interaction of the pre-S1 domain with its receptors [20].

The preC-C (precore-core) region encodes for hepatitis B core antigen (HBcAg) and hepatitis B e antigen (HBeAg) [19]. The P region encodes the viral polymerase enzyme which is involved in DNA synthesis and RNA encapsidation. The X ORF encodes the viral X protein which modulates the host-cell signal transduction and can directly and indirectly affect host and viral gene expression [21]. X protein activity is absolutely required for the in-vivo replication and spread of the virus [22].

Hepatitis B surface antigen (HBsAg) is the first detectable serologic marker following acute HBV infection [23]. Hepatitis B surface antigen usually remains undetectable beyond six months and persistence beyond this period implies chronic infection. The disappearance of HBsAg is followed by appearance of antibody to HBsAg (anti-HBs). In most patients anti-HBs persists for life thereby conferring long-term immunity.

Hepatitis B core antigen is not routinely detectable in serum of HBV-infected patients because it is sequestered within the HBsAg coat. However, antibody to HBcAg (anti-HBc) is demonstrable in serum beginning within the first two weeks after the appearance of HBsAg and preceding detectable levels of anti-HBs by weeks to months. In some patients, anti-HBs may not be detectable until after a "window" period of several weeks to months during which neither HBsAg nor anti-HBs can be detected. At this time, the serologic diagnosis of current or recent HBV infection can be made by detection of IgM antibodies against HBcAg (IgM-anti HBc) [17]. Isolated anti-HBc may also represent cross-reacting or false positive immunologic specificity. Anti-HBs and anti-HBc persist indefinitely in persons who have recovered from HBV infection.

Hepatitis B e antigen (HBeAg) appears concurrently with or shortly after HBcAg. Its appearance coincides with high levels of viral replication and infectivity. Hepatitis B e antigen becomes undetectable in self-limited HBV infection before the disappearance of HBsAg and antibody to HBeAg (anti-HBe) then becomes detectable coinciding with a period of relatively lower infectivity. Hepatitis B virus DNA (HBV-DNA) and polymerase are detectable during the period of viral replication [23].

The major routes of transmission of HBV are percutaneous via blood and blood products; vertical from infected mother to the baby; horizontal from infected family members and playmates and through sexual and physical contact with body fluids from infected individual. In the developing countries, the predominant modes of transmission are vertical (i.e. mother to child) and horizontal from infected family members and playmates. The early acquisition of this virus via these routes leads to chronicity of the infection since the immune response that usually clears the infection fails to take place or is too weak to be effective [24]. Also, response to anti-viral therapy to eliminate the virus has not been too successful in those who acquired the infection early in life because their immune system mounts a weaker response to the infection. This has been attributed to some degree of tolerance of the immune system to the viral antigens [24].

Hepatitis B virus and chronic kidney disease

In 1971, Combes *et al* described a 53-year-old man who developed membranous glomerulonephritis (MGN) with complexes of HBsAg and anti-HBs in the kidney following

blood transfusion [25]. Observations of greater-than-expected incidence of chronic HBsAg carriers among the patients with various forms of glomerulonephritides compared with the general population in different geographical areas tend to support the hypothesis of a pathogenetic association between chronic HBV infection and the glomerulonephritides [5]. The various morphological patterns of glomerulonephritis that have been associated with HBV include membranoproliferative glomerulonephritis (MPGN),membranous glomerulonephritis, mesangial proliferative glomerulonephritis, and proliferative glomerulonephritis [26-28].

To prove that a particular glomerulonephritis is aetiologically associated with chronic HBV infection, the following criteria need to be fulfilled: reproduction of the pathology in experimental animal infected with the virus; demonstration of HBV specific antigen(s) in the glomerulus; and disappearance of the pathology with eradication of the virus [27,29]. However, in practice this is not always possible making the definition of HBV – GN uncertain. This is because

- reproduction of glomerulonephritis and particularly the different morphological forms in infected experimented animals has not always been possible;
- the presence of HBV – specific antigens in the glomerulus may be due to antigen trapping within an area of glomerular damage and not necessarily due to a primary pathogenetic mechanism as suggested by the occasional observation of HBsAg in glomerular diseases not believed to be due to immune complex deposition such as focal sclerosis and minimal change disease; and
- eradication of the virus after the patient had developed glomerulonephritis is not always associated with disappearance of the kidney pathology [27,29].

Epidemiology of Hepatitis B - Associated Glomerulonephritides

The true incidence of HBV-associated glomerulonephritides remains controversial since the patients are not always symptomatic. This is borne out by studies demonstrating immune complex deposits in the kidneys of unselected patients with viral hepatitis in the absence of renal disease and by autopsy studies showing kidney lesions (MGN, MPGN) in 15 – 32 % of patients who died of acute or chronic HBV infection despite the absence of clinical evidence of renal disease [30].

There are striking differences in the prevalence and histological patterns of HBV – GN in different countries and in different age groups within the same country. The prevalent histological pattern reported in children with HBV–GN is membranous glomerulonephritis (MGN) with HBsAg prevalence rates varying between 55 % and 96 % [31-33]. Vos *et al* [34] showed that 24 % of black children with nephrotic syndrome seen between 1981 and 1985 in Johannesburg, South Africa, were HBsAg positive and all had MGN. Dreyer suggested that the high frequency of MGN in black patients in S. Africa might be related to the high HBsAg carrier rate in the black population since 15 to 17% of black children were HBsAg positive compared to 0.1 % of white children [35]. However, in Nigeria, Abdurrahman *et al* did not find any significant difference in the HBsAg carrier rate of nephrotic children when compared with the control group [36]. The prevalent histological pattern in HBsAg positive patients, however, was MPGN [36]. They, however, noted that the pattern of immunofluorescence and the histological varieties were similar to those in hepatitis B-associated nephrotic syndrome reported by other workers elsewhere suggesting a possible causal role of HBV in some cases of childhood nephrotic syndrome in Africa [36].

The prevalent histological patterns reported in adults were membranoproliferative and mesangial proliferative GN [37-38]. Lee *et al* [37] found that 87% of adults with MPGN in Korea were HBsAg carriers and Lai *et al* [38] reported a prevalence of 42 % in patients with mesangial proliferative GN in Hong Kong [5,39]. Hepatitis B associated glomerulonephritis were rarely encountered in France, United States of America and Canada [5]. The few reported cases had been mainly in the immigrants and minority population. Certain studies from New Delhi, Bulgaria and China did not show any significant difference in the prevalence of HBsAg in patients with glomerulonephritis compared with the normal population [5,40]. Awunor – Renner *et al* [41] found that 19.5 % of patients who presented with glomerular disease at the Ahmadu Bello University Teaching Hospital Zaria, Nigeria had hepatitis B surface (HBs) antigenaemia in contrast to 9 % of the matched control. Eight of the 16 patients with acute nephritic syndrome were carriers of HBsAg [41] Akinsola *et al* [26] found HBs antigenaemia in 33.3 % of their cases with chronic glomerulonephritides as compared to 6 % in the control population strongly suggesting a significant association between HBV and chronic glomerulonephritides. Hepatitis B antigenaemia was most prevalent in patients with asymptomatic proteinuria and nephrotic syndrome and the prevalent histological type associated with HBsAg was membranoproliferative GN [26].

Pathogenesis of HBV- associated glomerulonephritis

The pathogenetic mechanisms underlying the development of HBV-GN are unknown. However, different hypothesis have been put forward. All the three major HBV antigens, that is, HBsAg, HBeAg and HBcAg have been localized by immunofluorescence in the glomerular capillary wall in HBV-MGN. It is hypothesized that HBV – MGN results from subepithelial immune complex formation involving sequential localization of anti – HBe antibodies which are cationic followed by anionic HBeAg which is the only antigen with a size ($3 - 9 \times 10^4$ daltons) capable of penetrating the basement membrane [27,29] An alternative

pathogenic mechanism in HBV – MGN could involve the induction of autoantibodies to intrinsic glomerular antigens [27,29].

The pathogenesis of both HBV – MPGN and mesangial proliferative GN most likely involves mesangial and sub-endothelial passive trapping of HBV antigen-containing immune complexes. It is also possible that some of the mesangial proliferation in these lesions may be due to direct infection of the mesangial cell by the HBV [27,29]

Clinical features of hepatitis B virus-associated glomerulonephritides

HBV-MGN is commoner in children than in adults and occurs predominantly in males. Studies in the United States and South Africa have shown that it is predominant in the black population [5,34,39]. Patient usually presents with nephrotic syndrome or non-nephrotic proteinuria and macro – or microscopic haematuria [42]. Generally, there is no history or clinical evidence of ongoing liver disease except in rare cases. Spontaneous resolution can occur. Progression to chronic renal failure has also been documented. Hepatitis B surface antigen (HBsAg) and antibody to hepatitis B core antigen (anti-HBc) are almost always demonstrable in the circulation. About 60 – 80 % of patients also have circulating hepatitis B e antigen (HBeAg) [42].

The serum complement (C3 and C4) levels are depressed in 15 – 64 % of cases in some series while complement levels are normal in some series [42]. Immunofluorescent staining of the glomerular capillary wall is usually positive for IgG (100 %), C3 (75 %), IgM (50 %) and IgA (10 %) [42].

Hepatitis B virus associated-MPGN has been reported in adults and children [5,42] though it is commoner in adults. Patients present with proteinuria in the nephrotic or sub-nephrotic range, haematuria, elevated blood pressure and renal insufficiency [42]. Patients frequently have no history of clinical hepatitis despite a few who may have abnormal liver function. Serum complements C3, C4 are often depressed and circulating immune complexes are present [42].

Hepatitis B virus infection and dialysis

Shortly after the introduction of haemodialysis (HD), outbreaks of jaundice which were later attributed to viral hepatitis were reported in patients and staff in Europe and America [43-45]. These outbreaks led to the setting up of the Rosenheim Advisory Group in Britain in 1972 [46] and the Centres for Disease Control and Prevention (CDC) Committee on HBV control in 1977 [47]. The recommendations made by these two bodies in controlling HBV infections in dialysis setting included segregation of HBsAg – positive patients from HBsAg – negative patients; the use of dedicated machines for HBsAg – positive patients and regular serologic screening for HBsAg and anti – HBs in addition to routine cleaning and disinfection procedures [46,47]. The institution of above recommendations led to a significant decline in the annual incidence of HBV infections from 3.0 % in 1976 to 0.1 % in 1989 in America [48]. Also, the prevalence of HBV infection declined from 7.8 % to 1.4 % in the patients; and from 2.4 % in 1972 / 1973 to 0.3 % in 1989 amongst the staff [48].

Transmission of HBV infection can occur in dialysis setting through contamination of equipments, environmental surfaces and the hands of staff (if the same staff care for both HBsAg - positive and negative patients in the same shift) and through the use of multiple dose vials of drugs [49].

In a survey of the renal units in United Kingdom, the prevalence of HBsAg in patients on maintenance haemodialysis and peritoneal dialysis were 0.53% and 0.54 % respectively [49]. Oguchi *et al* [50], in a survey of eleven Japanese HD units found HBsAg positivity of 1.6 %. However, unlike the developed countries, the prevalence of HBsAg is still high in developing countries. Reported prevalence rates of HBsAg positivity were 8 % in Kenya [51], 10.9 % in Saudi Arabia [52], and 7.5 to 28 % in Brazil [53]. In Ibadan, Nigeria, 13 % of predialytic chronic renal failure patients were HBsAg positive [54]. In a survey of 22 dialysis centres from Santa Catarina State, south of Brazil, 10 % of the patients were HBsAg positive compared to 2.7 % and 2.7 % in HD health care workers and healthy controls respectively [55]. The risk for a patient to become HBV positive increase 1.47 times each month of dialysis; 1.96 times if dialysis unit reuses the lines and filters 10 times or more compared with HD units which reuse less than 10 times. In addition, the risk of becoming seropositive is 3.42 times if the number of patients per worker is more than five [55].

Hepatitis B virus infection and kidney transplantation

Studies on the effect of HBV infection on graft and recipient survival have shown variable results [56-57]. Fornairon *et al* [56] evaluated 151 HBsAg positive renal transplant (RT) recipients after a median follow-up of 125 months. Renal allograft survival was significantly reduced among those with HBV infection when compared with 1247 uninfected RT recipients ($P = 0.0006$) [56]. Histological deterioration in liver disease was noted in 85 % of the patients accompanied by cirrhosis in 28 % and by hepatocellular carcinoma in 23 % of the patients with cirrhosis. However, there was no difference in overall mortality in the two groups [56]. On the other hand; Correa . did not find any significant difference in the graft survival of the HBV infected compared with the non-infected group. Also, there was no significant difference in the 10 year patient survival in the HBV infected group (77.8 %) compared to the non-infected group [57].

Treatment

The goal of therapy in patients with HBV infection are reduction in the level of viraemia ; amelioration of liver

dysfunction and remission of the kidney disease [19,58,59]. The drugs that have been approved for the treatment of HBV are interferon (IFN) and nucleoside analogues such as lamivudine and adefovir.

Interferons inhibit replication of many viruses by both direct antiviral mechanisms and amplification of specific and non-specific immune responses to viral proteins. Interferon acts by binding to IFN cell surface-receptor subunits leading to their dimerization and the activation of the receptor-associated Janus-activated kinase 1(Jak 1) and tyrosine kinase 2 (Tyk 2) [60,61]. The activated kinases phosphorylate the signal transducers and activation of transcription proteins 1 and 2 (STAT 1 and STAT 2) [62].

The activated STAT 1 / 2 complex is then translocated to the cell nucleus where it combines with IFN-regulatory factor 9 (IRF-9) to form a complex that binds to IFN-stimulated response elements on cellular DNA leading to expression of multiple IFN-stimulated genes which establish antiviral state within the cell [63]. Interferons also promote memory T-cell proliferation, prevent T-cell apoptosis and stimulate natural killer-cell activation and dendritic-cell maturation [64]. Interferon also up-regulates the production of major histocompatibility complex class-I and class-II peptides, and might promote a T-helper-1 (T_H1) over a T-helper-2 (T_H2) phenotype [62].

A meta-analysis of 15 randomized placebo-controlled studies of IFN-alpha treatment in HBeAg positive patients by Wong *et al* showed loss of HBV-DNA, HBeAg and HBsAg in 37 %, 33 % and 7.8 % of patients compared to 17 %, 12 % and 1.8 % respectively in controls [65]. Factors associated with favourable outcome following IFN therapy include alanine aminotransferase (ALT)levels > 200 U / L, serum HBV-DNA levels of < 100pg / mL, liver histology showing active hepatitis, short duration of infection (especially if < 1 year) and absence of severe comorbid illness or immunosuppression [3]. On the other hand, male sex, length of chronic state, Asian origin, precore mutations, homosexuality and HIV co-infection have been associated with poor response to IFN [66].

Interferon has been used in HBV – GN [59]. Its use has been associated with partial or complete remission of the kidney disease. Interferon is contraindicated in the transplant patient because of its immunomodulatory effects which can induce rejection episodes [67]. Spontaneous remission occurs in 30 – 60 % of HBV – MGN and is not uncommonly associated with seroconversion from HBeAg to anti-HBe [68]. However, loss of HBeAg is not always associated with remission of the kidney disease.

Nucleoside analogues act by causing chain termination and thus inhibiting viral replication following their incorporation into newly synthesized HBV-DNA [66]. Also, they can competitively inhibit the DNA-dependent and reverse transcriptase activity of the viral polymerase [66]. The analogues are metabolized within the cells into the active triphosphate before exerting their effects.

Lamivudine is a synthetic nucleoside analogue which is metabolized within hepatocytes to the active triphosphate by stepwise addition of phosphate groups. It acts by terminating viral DNA synthesis and competitively inhibiting the viral polymerase / reverse transcriptase. In addition, there is evidence to suggest that lamivudine treatment may overcome cytotoxic T cell hyporesponsiveness seen in chronically infected patients [69]. Lamivudine can be used in dialysis and transplant settings [70]. The principal limitation of lamivudine monotherapy is the development of drug resistance which is mediated largely by point mutation at the YMDD motif at the catalytic centre of the viral reverse transcriptase [19].

Adefovir is a phosphonate of an acyclic nucleotide analogue. Adefovir, aside from being a DNA chain terminator is also thought to stimulate natural killer-cell activity and to induce endogenous interferon production [71]. It has been shown to have good efficacy against HBV in HBeAg positive patients with reduction in viraemia, enhancement of HBeAg seroconversion and histologic improvement in the liver [72]. The drug also effectively inhibits the replication of lamivudine – resistant HBV mutants, both in vitro and in vivo [73]. However, its role in the treatment of HBV – GN and in dialysis and transplant recipients is yet to be defined.

Other nucleoside analogues that have been tried in the treatment of chronic HBV infection but yet to be approved by the Food and Drug Agency include entecavir, famciclovir, ganciclovir, clevudine, lobucavir, telbivudine and tenofovir [66]. The above mentioned drug have not been tried in the treatment of HBV – GN.

Future potential treatments

Immunotherapy involving therapeutic vaccination and deoxyribonucleic acid (DNA)-based vaccines has also been tried in the treatment of chronic HBV infection [66]. Therapeutic vaccination involves the use of pre-S2 / S or S vaccine. The use of HBV vaccine promotes production of antibodies and a Th2-based immune response. However, for therapeutic vaccination to be effective, both humoral and cytotoxic T cell responses may be necessary to eradicate infected cells. In a controlled study of 118 patients receiving GenHavac B (Pre-S2 / S), Recombivax (S) or no vaccine, seroconversion of HBeAg to anti-HBe was seen in 13.3 % of vaccines versus 3.6 % of controls after 6 months of follow-up [74]. The seroconversion rate gap, however, narrowed to 18.9 % versus 12.5 % after 12 months of follow-up. None of the patients lost HBsAg [74].

Peptide-based T-cell vaccines have also been tested in patients chronically infected with HBV. The vaccine induced CTL activity, which was not sufficient to clear the infection [75]. DNA-based vaccines involve the use of plasmids encoding HBV antigens. Following injection into the body, the encoded proteins are expressed in their native conformation in vivo and they undergo appropriate post-translational modifications. This ensures that correct epitopes are presented to the immune system. Plasmid DNA

immunization results in the generation of humoral immune responses and induction of potent CD8+ CTL responses [76]. Evaluation of a DNA vaccine against HBV in healthy human volunteers showed that the vaccine was safe, well tolerated and produced preferentially Th 1 helper cell responses [77]. Humoral anti-HBs responses were however weak. None of these vaccines have been licensed for use in patients with chronic liver disease.

Immunization against hepatitis B virus infection

In spite of the fact that patients already on HD or RT programmes and those with CRF have suboptimal antibody response and poor ability to maintain protective antibody levels following conventional immunization, immunization against HBV infection is still recommended in these groups of patients [78,79]. This will ensure that in the event of an outbreak the least number of patients is involved and progression to the chronic carrier state does not occur in case of any breakthrough infection [49]. Despite the proven benefits of HBV immunization in these groups of patients, not all patients are immunized. A recent survey of renal units in United Kingdom showed that 29 % of the units did not immunize any patient group and of the 55 units (71 %) that provided immunization, 70 % gave the recommended higher dose of 40 µg whereas 30 % gave the previously recommended dose of 20 µg [80]. Most (72 %) used the earlier schedule of doses at 0, 1 and 6 months instead of the recommended accelerated schedule of 0, 1, 2 and 12 months [80]. A recent study suggest that three 20µg doses of the vaccine may be suitable for children and adolescents with CRF who are not on immunosuppressive medication [81]. Ninety nine percent of the 66 patients (children and adolescents) administered three doses of the hepatitis B vaccine Recombivax HB had a protective titre of ≥ 10 mIU / mL against HBsAg. The response rate was high in predialysis (100%) compared to dialysis (64 %) and renal transplant recipients (50 %). Eighty eight percent of 57 fully vaccinated patients tested 12 months after the first dose retained ≥ 10 mIU / mL anti- HBs titre [81].

Staff working in renal units in clinical contact with patients or their environment and carers of patients with CRF should be screened and those negative for HBsAg should be offered immunization. Any staff found to be HBsAg positive should be further tested for HBeAg and if found to be negative should have their HBV DNA levels determined. Any health care worker who are either HBeAg positive or are HBeAg negative with an HBV DNA level exceeding 10^3 genome equivalents / mL should not undertake clinical duties on renal dialysis units [42]. Staff and carers of patients with CRF should have 20 µg of the vaccine at 0, 1 and 6 months. Table 1 summarizes the measures for preventing HBV transmission in dialysis and renal transplantation settings.

In conclusion, hepatitis B virus infection is still prevalent in sub-Saharan Africa. Control of HBV infection in the population by immunization can lead to reduction in

Table 1: Primary measures for preventing hepatitis B virus transmission in renal dialysis and transplantation settings*

- Patients with chronic renal failure, on dialysis or renal transplantation programmes should be immunized against HBV
- Staff attached to renal units who have direct contact with patients' blood or blood stained body fluids or with patients' tissues should be immunized
- Carers of patients with chronic renal failure particularly those involved with the dialysis process should be immunized
- Patients with HBV infection should be dialyzed in a separate room or a separate area from non – infected patients. The separated areas for HBV infected and non – infected patients ideally should be demarcated with clear boundaries, which may include permanent walls or glass partitions, or more adaptable arrangements such as tall moveable washable screens
- There should be sufficient storage space in the HBV area for sterile items, fluids and other equipments for staff to perform the majority of their daily duties without having to cross between areas to collect equipment or to perform other tasks.
- Dedicated machines should be used to dialyse HBV infected patients
- Whenever possible, staff should be assigned to work only with patients infected with HBV in the segregation area, or with uninfected patients in any one shift. When infected and uninfected patients have to be cared for by the same staff, this should be done by experienced staff who should adhere rigorously to infection control procedures.
- Multi-use vials of drugs should only be used for individual patients
- All staff should cover cuts and abrasions with water – proof dressing
- Staff with extensive epithelial deficiency such as eczema should not work on renal units when their skin lesions are active or if there are extensive breaks in the skin surfaces.
- Staff should wear protective clothing (gloves, aprons and facial protections) whenever there is a risk of exposure to blood or body fluids
- Gloves and aprons should be changed and hands decontaminated between each patient and between different caring activities for the same patient.
- All exposed surfaces in and adjacent to each patient's treatment station should be washed with neutral detergents and hot water and thoroughly dried between patient treatment; where there is visible blood, disinfection should be carried out
- Adequate treatment space and staffing should be provided to ensure safe working practices
- The dialysis fluid circuit of the dialysis machine should be decontaminated between patients according to the method recommended by the manufacturer. External surfaces of machines should be disinfected after each use by a HBV infected patient. Surfaces of all machines should be disinfected daily
- Dialysers should not be re – used unless specified by the manufacturers

* *Adapted from reference 49.*

HBV –associated glomerulonephritides. Interferon and nucleoside analogues have been used successfully in the treatment of chronic liver disease. While the use of interferon has been associated with partial or complete remission of HBV-GN, its use is contraindicated in transplant patients because of its immuno-modulatory effects which can induce rejection episodes. Lamivudine, however, can be used in transplant patients. Also, strict adherence to asepsis will help in preventing HBV transmission in dialysis and transplantation settings which may in turn impact positively on graft and host survival. Finally, patients with CKD should be offered immunization with emphasis on adequate dose and dosing.

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