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REVIEW ARTICLE

Infections in hemodialysis: a concise review. Part II: blood transmitted viral infections.

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Abstract

Hemodialysis (HD) patients are particularly predisposed to infections. It seems that the HD procedure per se as well as disturbances in both innate and adaptive immunity significantly contribute to this susceptibility. Infections are the major cause of morbidity and the second cause of death following cardiovascular events in HD patients. Episodes of bacteremia and pneumonia account for the majority of severe infections in this population. In addition to these bacterial infections another common problem in HD units is the blood transmitted viral infections, particularly infections caused by hepatitis B virus, hepatitis C virus and Human immunodeficiency virus. A number of safety concerns exist for limiting the spread of these viral infections among HD patients and the staff of the unit. The aim of the present review is to present in a concise albeit practical form the difficult aspect of infections in HD. For practical reasons the review is separated in two parts. The previous first part covered bacteremia and respiratory infections, while the present second part covers blood transmitted viral infections. Hippokratia 2011; 15 (2): 120-126

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Hemodialysis (HD) procedure per se as well as disturbances in both innate[1-3] and adaptive immunity[4-6] make HD patients susceptible to infections. Infections are the major cause of morbidity and the second cause of death following cardiovascular events in HD patients. Interestingly, death risk from cardiovascular events significantly increases after hospitalization due to infection. Episodes of bacteremia account for the majority of severe infections in this population, while episodes of pneumonia follow[7]. The annual mortality due to bacteremia is 100-300 times higher in HD patients compared to the general population. Even when age, race, sex, diabetes and record errors are taken into account, mortality owing to bacteremia is still 50 times higher[8,9]. Besides bacterial infections, another common problem in HD units is the blood transmitted viral infections, particularly infections caused by hepatitis B virus (HBV), hepatitis C virus (HCV) and Human immunodeficiency virus (HIV). Due to the nature of the HD procedure, safety concerns exist for limiting their spread among HD patients and the staff of the unit. In addition, the natural history of all these infections, the available treatments and the response to vaccines differ from what is known for the general population. There are many appreciable reviews that analyze rather extensively each infectious agent separately[10-15]. The aim of the present review is to present in a concise albeit practical form a global update of the difficult aspect of infections in HD. In the present second part of the review blood transmitted infections, which are present in all HD units, are discussed.

Hepatitis B and hemodialysis

It is estimated that approximately 350 million people are chronic hepatitis B virus (HBV) carriers worldwide[16]. Consequently, most HD units treat chronic HBV carriers. Interestingly, because of the known acquired immunity disturbances in this population[5], after the initial HBV infection, 60% of hemodialysis patients become chronic carriers, while the respective percentage in the general population is only 5%[17-19]. Fortunately, HBV carriage does not significantly affect prognosis of HD patients. Although 30% of HBV carriers develop histologically confirmed chronic hepatitis, only 5% die from liver disease[20,21]. However, life threatening exacerbations and increased rates of liver disease were reported in renal transplant recipients who were asymptomatic during HD[22-26]. In a meta-analysis chronic HBV infection was associated with an increased risk of death (RR 2.49) and graft loss (RR 1.44)[27].

Serology helps to determine the HBV status of HD patients (Table 1). A HBsAg, anti-HBc and anti-HBs negative patient is susceptible and needs vaccination. A HBsAg negative but anti-HBc and anti-HBs positive patient is immune due to natural infection, while a HBsAg and anti-HBc negative but anti-HBs positive patient is immune due to vaccination. HBsAg, anti-HBc and IgM anti-HBc positivity without anti-HBs indicate an acutely infected patient, while HBsAg, anti-HBc positivity without IgM anti-HBc and anti-HBs indicate the chronic carrier state. The situation is more complex when a patient

Table 1: Hepatitis B serology

Serological markers	Interpretation
HBsAg (-) anti-HBc (-) anti-HBs (-)	Susceptibility
HBsAg (-) anti-HBc (-) anti-HBs (+)	Immunity because of vaccination
HBsAg (-) anti-HBc (+) anti-HBs (+)	Immunity because of natural infection
HBsAg (+) anti-HBc (+) anti-HBs (-) IgM anti-HBc (+)	Acute infection
HBsAg (+) anti-HBc (+) anti-HBs (-) IgM anti-HBc (-)	Chronic infection
HBsAg (-) anti-HBc (+) anti-HBs (-)	False positive anti-HBc test or Resolved acute infection or Resolved infection or "Low level" chronic infection
HBeAg (+) HBV DNA (+)	Active virus replication

is HBsAg and anti-HBs negative but anti-HBc positive. The above serology could mean resolved infection which is the most common, or resolving acute infection, or false positive anti-HBc, or "low level" chronic infection[28]. The last case is of particular interest and a Canadian study showed that although in 241 hemodialysis patients only 2 (0.8%) were HBsAg positive, among the rest 239 patients, 9 (3.8%) were found to be HBV-DNA positive with PCR[29]. Thus HBV-DNA test is useful for anti-HBc positive patients who are also negative for HBsAg and anti-HBs. Additionally, nowadays hidden hepatitis is revealed with nested PCR for the pre-S/S, pre-core/core and X regions of the HBV genome[30].

When HBV carriage is confirmed, the follow up of HD patients includes serum alanine transaminase (ALT) and aspartate transaminase (AST) every 1-2 months, alpha-fetoprotein (AFP) every 3-4 months, albumin and prothrombin time. The hypoaminotransferasemia that characterize HD patients should be taken into consideration, since the normal ALT and AST levels are less than 27 IU/L and17 IU/L in this population[31]. Interestingly, the absence of HBeAg does not necessarily exclude viral replication if there is a mutation of the pre-core/core gene inducer[32]. HBV-DNA should be tested at least annually and liver biopsy is recommended when specific treatment is to be started or prior to renal transplantation[33,34].

Significant viral replication, with more than 100000 copies/ml with PCR, indicates the need for treatment[35]. Despite the limited data, interferon A seems to be beneficial[36]. However, the increased rate of side-effects in HD patients, mainly anemia and cachexia, establishes nucleoside analogues as the treatment of choice[37,38]. Nucleosides analogues should be administered for at least one year. Lamivudine at a dose of 10mg per day is particularly effective in HD patients, since it suppresses viral replication and transaminasemia in 80% of patients[39-41]. Unfortunately, 15 % of patients develop resistance after one year of treatment and 30% after two years due to mutation of RNA-dependent HBV-DNA polymerase[42-44]. Telvivudine at a dose of 600mg every 96 hours is characterized by much less resistance development compared to lamivudine and can be used as first line treatment[45]. New but not yet tested in HD patients nucleosides analogues remain to be tried.

For preventing intra-unit HBV spread, the usual precautions for blood transmitted infections should be strictly applied. Blood could be present even on surfaces that seem very clean with naked eye[46]. Despite some doubt[47,48], patients should be hemodialyzed in separate rooms[49], since HBV is found in high titers and is potentially infectious for more than 7 days in the environment. In comparison, hepatitis C virus (HCV) is less infectious and survives for a shorter period of time, while Human immunodeficiency virus (HIV) is far less infectious and cannot survive in natural environment[50-52]. The risk of infection after contaminated needle stick exposure is about 6% if the patient is HBeAg negative and about 30% if the patient is HBeAg positive[53]. If not vaccinated, which is unacceptable for the HD unit staff, the individual should receive a dose of HBV immune globulin (HBIG) (0.6mg/kg) and start vaccination. If the individual is vaccinated and the anti-HBs levels are higher than 10 IU/ml no measures are required. For the vaccinated individual with anti-HBs levels below 10 IU/ml a dose of HBIG plus a repetitive vaccine dose are indicated. Finally, two HBIG doses are required for individuals who did not respond after two complete series of vaccination[54].

Vaccination against HBV is also an effective measure, since vaccinated patients have 70% less possibility to become HBV carriers[55]. Unfortunately, due to the impaired immune function of HD patients 3-6[56], response rates determined as anti-HBs titres higher than 10 IU/L are smaller in HD patients than in the general population. Despite the administration of double vaccine doses and of an extra dose in HD patients, response rate is about 50-60%, while the response rate in the general population is higher than 90%[57,58]. Some authors referred a higher, but still less than in the general population, vaccine-induced seroconversion rate (75-80%), possibly due to differences in the patients' selection criteria[56,59]. All doses of the vaccine should be repeated in patients who have not responded 1-2 months after complete first vaccination series[60]. Nevertheless, only one dose is required in patients with initial anti-HBs levels greater than 10 IU/L due to successful response to vaccination or natural infection who now present with reduced anti-HBs levels[61,62]. Vaccination should be performed as soon as possible in the course of chronic renal failure since response is associated with the degree of renal function[63]. Finally, new

vaccines against HBV containing new immune adjuvants are promising. For example, the HBV-AS04 vaccine was found to provide better initial response rates (78% vs. 51%) and also greater duration of response during the 42 months study period[64].

Hepatitis C and hemodialysis

There are about 170 million hepatitis C virus (HCV) carriers worldwide and HD patients belong to a high-risk population[65]. A meta-analysis revealed that in HD patients HCV carriage is associated with 1.57 times increased risk of death. Liver cirrhosis and hepatoma contribute to the increased mortality[66].

Typically HCV carriage is indicated by the presence of anti-HCV antibodies, which currently are assessed in the serum with third generation ELISA. Optimally, a positive result could be confirmed with RIBA (recombinant immunoblot assay) due to the higher specificity of this assay[67,68]. Detection of HCV-RNA with PCR also confirms the diagnosis of HCV carriage and indicates viral replication as well. However, it should be noted that in the course of HCV carriage there are intervals without detectable HCV-RNA in the serum[69]. Recently, HCV core Ag detection with ELISA can be used for the diagnosis of HCV carriage[70-72].

Interestingly, a patient can be anti-HCV positive, but HCV-RNA negative. Such results could mean that the patient has been cured or reflect interrupted viremia that is common in the course of HCV carriage. A false positive ELISA or a viremia below the PCR lower detection limit could also be responsible[73-75]. In the opposite situation, a patient can be anti-HCV negative, but HCV-RNA positive. This could be the result of inability to develop a satisfactory antibody titre due to the immune dysfunction that accompanies HD or simply reflect the window between infection and antibody production. Certainly, a false positive ELISA may also be the cause[76-78].

Currently, it is suggested to use HCV-RNA detection for diagnosis of HCV carriage in areas or HD units with high HCV prevalence, while anti-HCV antibodies detection is better to be used in areas or HD units with low HCV prevalence. A positive anti-HCV test should always be followed by a HCV-RNA test. The latter should also be applied in case of hypertransaminasemia even if the anti-HCV test is negative. The screening with the one or the other method should be repeated every 6-12 months[79].

Antiviral treatment is indicated in patients with chronic kidney disease –besides transplanted patients – with acute HCV infection who did not have negative PCR after 12 weeks. Patients from transplantation lists that meet the above criteria should be treated. Regarding the HCV-infected kidney transplant recipients, it is suggested that treatment should be considered only when the benefits of treatment clearly outweigh the risk of allograft rejection due to interferon A based therapy. In the latter patients, such a treatment could be applied in case of fibrosing cholestatic hepatitis or life-threatening vasculitis. Generally, the desired serologic response to treatment is a negative HCV-RNA PCR 6 months after treatment is completed. If a desired serologic response is achieved, retesting for HCV-RNA every 6 months is recommended[80].

Currently, routine ribavirin treatment is contraindicated in HD patients[81] and small trials showed increased rate of adverse effects with pegylated interferon A[82,83]. Thus the only available treatment is interferon A. A meta-analysis of 20 studies showed that treatment with interferon A led to a desired serological response in 41% of patients, while 26% of them discontinued the treatment because of side-effects. The results were better with doses greater or equal to 3000000 units 3 times per week. However, higher doses were associated with more frequent discontinuation of the drug due to adverse effects. Lower HCV-RNA titers and transaminase levels and absence of cirrhosis at the initiation of treatment were associated with a better prognosis[84].

In order to prevent the intra-unit spread of HCV, adhesion to general precautions for blood transmitted infections is required. Despite the existing doubts[85,86], HCV positive patient isolation or use of separate machines are not officially recommended[49,87-89]. The risk of infection due to contaminated needle stick exposure is about 1.8 % and unfortunately there is no preventive post exposure treatment available[53].

Human immunodeficiency virus and hemodialysis

The prevalence of Human immunodeficiency virus (HIV) positivity varies and is dependent on the region where the dialysis unit is located[90,91]. In the year 2000 1% of patients on dialysis in the USA has reached end-stage renal disease (ESRD) due to HIV associated nephropathy (HIVAN)[92]. HIVAN shows a predilection for black race[93,94] and accounts for the majority (65%) but not all of the ESRD cases among HIV positive patients[95].

All HD patients should be tested for HIV since prompt diagnosis, monitoring and timely initiation of Highly Active Anti-Retroviral Therapy (HAART) consisted of three or more highly potent anti-HIV drugs, commonly reverse transcriptase inhibitors and protease inhibitors, improves prognosis. A positive ELISA must be confirmed with western blotting as in general population. Among patients with positive ELISA and moderately positive western blotting, up to 4.5% of results can be false positive. This possibility is increased in cases of blood transfusions or renal transplantation. It is clear that, in case of positive results, serum HIV-RNA detection is mandatory[96].

Adhesion to general precautions for blood transmitted infections is adequate for preventing intra-unit spread of HIV and CDC does not recommend patient isolation or separate machines[49]. However if precautions are overlooked the results can be disastrous[97, 98]. The risk of infection after contaminated needle stick exposure is about 0.3%[99,100]. Preventive post-exposure treatment should start immediately. It includes 2-3 anti-retroviral drugs for a 4 weeks period and it reduces the risk of infection by 80%. The individual should be checked for HIV 0, 1, 2, 3

and 6 months after exposure[101-103].

In HIV positive HD patients native arteriovenous fistula creation should be encouraged since grafts show increased thrombosis and infection rates in these patients, possibly because of intravenous drug abuse[104,105]. However, arteriovenous grafts are preferred to CVC due to high infection rates of CVC[106]. Anemia is another common problem in these patients. Frequent infections and HAART toxicity have been incriminated[107]. Increased cardiovascular risk is another adverse effect of long lasting HAART administration[108].

The prognosis of HIV positive HD patients has significantly improved. HAART[109], disease stage at initiation of dialysis[110] and CD4 lymphocyte count[111] are the major prognostic factors. In 1980 mortality was 100% for the first year[110]. In the USA, the one-year survival has increased from 56% for those who started dialysis in 1990 to 74% for those who started in 1999[112]. Finally, in a recent study from France, no difference in one year survival was found between HIV positive and HIV negative patients[113]. All of the above benefits are mainly attributed to HAART, which must include the proper drugs given at the right time and at the right doses. Otherwise, control of viremia might be impaired or toxicity can be significant resulting in increased mortality. Cooperation with other specialists is mandatory[114-116].

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