REVIEW ARTICLE

Infections in hemodialysis: a concise review - Part 1: bacteremia and respiratory 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 present first part covers bacteremia and respiratory infections, while the second part will cover blood transmitted viral infections. Hippokratia 2011; 15 (1): 12-17

Key Words: hemodialysis, infection, bacteremia, pneumonia, influenza, H1N1, tuberculosis, review

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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 first part of the review bacteremia and respiratory infections, which account for the most of the mortality and morbidity due to infections in HD, are discussed.

Bacteremia in hemodialysis

Most episodes of bacteremia are associated with vascular access and especially with central venous catheters (CVC). According to the HEMO study, in a population where 7.6% of subjects had a CVC, 32% of hospitalizations for vascular access infection were attributed to CVC[16]. The risk of infection from CVC is estimated to be 10 times higher compared to arteriovenous fistula infection[17]. Regarding the type of CVC some studies doubted the benefit from cuffed CVC use compared to non-cuffed CVC[18-24], while others showed that cuffed CVC are better[25-29]. Currently cuffed CVC are preferred and Klevens et al demonstrated that vascular access associated bacteremia rate is 0.3 per 100 patient-months for native arteriovenous fistula, 0.7 per 100 patient-months for arteriovenous grafts, 4.6 per 100 patient-months for cuffed CVC and 7.3 per 100 patient-months for non-cuffed CVC[30]. CVC with silver in their cuff show no apparent advantages[31], while CVC impregnated with antibiotics although beneficial in the intensive care unit, have not been tested in HD[32].

Coagulase negative Staphylococcus (S.) aureus and recently S. aureus species resistant to methicillin or vancomycin (MRSA or VRSA) are the most common bacteria responsible for CVC associated bacteremia, culprits. Less often, Enterococci and Gram negative bacteria are responsible[33-37]. For the diagnosis of CVC associated bacteremia and identification of the responsible microorganism, typically CVC removal, as well as blood and catheter tip cultures are required. Alternatively, a 4 times

higher number of colony forming units (cfu) in blood cultures drawn from the CVC compared to peripheral venous blood culture lead to a diagnosis of CVC- associated bacteremia with a sensitivity of 94% and a specificity of 100%. A bacterial number higher than 100 cfu/ml in cultures obtained from the CVC and the concomitant development of the same bacterium in peripheral venous blood culture is also a strong indication[38]. Finally, a more rapid bacterial growth in cultures obtained from the CVC compared to peripheral venous blood culture can diagnose CVC related bacteremia with a sensitivity of 85% and a specificity of 91%[39].

The empirical initial regiment for treating CVC associated bacteremia includes vancomycin (20 mg/kg/wk) and gentamycin (1-2 mg/kg/HD) until culture results are obtained[40,41]. The widespread use of vancomycin has led to increased number of infections by vancomycin resistant enterococci, which could transfer via plasmids the above resistance to S. aureus. Therefore, other studies using cephazoline administration (2-3 g/HD) were performed with successful results[42,43]. Taking into account the high rates of infection with MRSA strains, about 100 times more often than in the general population, it seems wiser that the empiric regiment should be initially preferred and any changes should be performed after the results of blood culture and antibiotic sensitivity become available [33,37,44]. The antibiotic treatment should generally last for 3 weeks and one week after discontinuation of antibiotics a new blood culture should be obtained. Treatment should be prolonged for at least 4 weeks if a metastatic infection is suspected or if a blood culture remains positive 2 -3 days after initiation of treatment[40,41].

Regarding the fate of CVC, catheter removal is preferred but catheter preservation could be attempted in hemodynamically stable patients without subcutaneous tunnel infection in whom creation of another vascular access is extremely difficult. In one study, 32% of CVC were preserved without a significantly increased rate of metastatic infection from the delayed removal of the rest 68% due to persistent fever or recurrent bacteremia[24]. Thus according to this study, an attempt for catheter preservation is safe and successful in one third of cases. However in another study, where S. aureus was the cause of infection, 41% of CVC were preserved but serious complications were observed in 10 % of all. The percentage of serious complications was unacceptable high (25%) in patients who were febrile within 48 h and finally had their CVC removed[45]. Thus, when S. aureus is isolated from blood cultures the risk for serious complications from an attempt for catheter preservation is high and catheter removal is indicated.

The strategy of CVC replacement by using a guide wire has also been tried. The rationale is based on the hypothesis that adhesion of bacteria to the catheter walls, the so-called biofilm, is responsible for antibiotic treatment failure. In relevant studies, clinically stable patients who became afebrile after 48 h of treatment and had no subcutaneous tunnel involvement were included. 50% of the initially enrolled patients required catheter removal. Catheter replacement was performed to the rest and treatment was continued for 3 weeks. The result was positive in 90 and 80% of cases after 45 and 90 days respectively[46-48]. Staphylococcus aureus infection was associated with worse results. The outcome was not satisfactory when Enterococcus Spp. or Candida Spp. were responsible as well[20,47].

Prevention strategies have also been developed. Nasal Staphylococcus carriage in HD patients and HD unit staff has been incriminated for CVC associated bacteremia and its suppression or eradication with intranasal mupirocin (0.5 g, twice daily for 5 days) showed good results[49,50]. Application of antibiotics or antimicrobial agents on the CVC exit site, such as mupirocin[51], polysporin (bacitracin-polymyxin-gramicidin)[52] and povidone-iodine[53] is also promising for preventing extra-luminal spread of bacteria. A meta-analysis revealed that local application of antimicrobial agents reduces both CVC associated bacteremia (0.10 vs. 0.45 episodes/100days), and exit site infection (0.06 vs. 0.41 episodes/100days)[54]. However, emerging resistance to locally applied antibiotics constitutes a major problem[55,56].

Strategies for preventing CVC associated bacteremia due to intra-luminal spread of bacteria have also been developed. A meta-analysis, which included 816 CVC and 624 patients, revealed that catheter lock with antibiotics or antimicrobial agents reduces the risk of bacteremia by 7.72 times[57]. Again emerging resistance to locally applied antibiotics constitutes a major problem. Side effects, such as ototoxicity from aminoglycosides are also a concern. Taurolidine seems to be a safe antimicrobial agent, while dense citrate solutions are not recommended by the FDA due to rare but serious complications (QT prolongation)[58-60].

Timely creation of a native arteriovenous fistula or at least of an arteriovenous graft is the best solution since it is confirmed that change from CVC to fistula or graft decreases the risk of death significantly[61.] Unfortunately, most patients still start HD with a CVC and a permanent access placement after dialysis initiation is often delayed[62]. It is obvious that the nephrology community has to strengthen its efforts to this direction.

Respiratory infections in hemodialysis

Pneumonia is the second more common cause of severe infection in the HD population[7]. Compared to the general population, pneumonia associated death rates are 14-16 times higher in HD patients[63,64]. The most common causes of pneumonia in HD patients are pneumonia of community, mainly by Streptococcus pneumoniae, seasonal influenza and bacterial pneumonia secondary to influenza[63].

The treatment of pneumonia from Streptococcus pneumoniae is the same as in general population and a vaccine is available. In a meta-analysis of 26 studies about the efficacy of the polysaccharide vaccine against Streptococcus pneumonia a satisfactory initial serologic

response was observed. In studies which lasted more than 6 months a more rapid decline in antibody titer was observed compared to the general population[65]. Current guidelines recommend vaccination of all HD patients and revaccination after 5 years[66].

Influenza outbreaks-flares affect 10-20% of the general population but in case of pandemic 50% might be affected[67]. Despite reduced immune response to the vaccine against influenza in HD patients, the vaccine is believed to provide sufficient protection and should be performed annually[68].

Regarding the last very virulent H1N1 influenza A strain, a study performed in 602 HD units of Fresenius Medical Care included 30288 patients in Europe and Middle East, 20262 in South America and 815 in Africa. From 30 of June to 3 of September 2009, 306 cases were reported from 85 units. The mean age of the affected HD patients was 52.7±17.7 years and the symptoms included fever (94.4%), cough (78.8%) and myalgia or arthralgia (69.3%). 87% of the affected patients received treatment with oseltamivir. 103 (34%) patients were hospitalized, 69 with pneumonia. The total mortality was 5% and the risk of death was 3 times higher when diabetes and heart disease were also present[69].

HD patients belong to high risk groups[69,70], and suspected cases should start treatment within 48 hours, many times before the final identification of H1N1 influenza A strain, better performed with PCR[70-73]. The neuroaminidase inhibitor oseltamivir at a dose of 30 mg after every HD session is the treatment of choice[74], although there is a small percentage of resistance[75]. Unreasonable use of oseltamivir should be avoided in order to prevent an increased resistance rate, which occurred with former antiviral agents like amantadine[76,77].

Vaccines against H1N1 influenza A strain with or without the immune adjuvant MF59 are effective[78,79]. Although vaccination of the general population is recommended, priority should be given to high risk groups such as HD patients. Health care workers should also have priority to vaccination[80,81]. For the general population a single dose of the vaccines in persons older than 10 years is adequate, while two doses with a 4 week interval between them is recommended in subjects 6 months to 9 years old and some high risk groups[81]. Interestingly, two doses of the vaccine is not officially recommended in HD patients[81], possibly due to the experience acquired from the vaccination of this population for common seasonal influenza. A second dose of seasonal influenza vaccine showed no benefit to HD patients[82-84]. Regarding vaccine safety, in the USA no difference was observed in side-effects between the vaccine against H1N1 pandemic influenza and seasonal influenza[80,81,85]. However, vaccines available in the USA do not contain the immune adjuvant MF59 or AS03 or squalene. The concern about the safety of the vaccine containing squalene is derived from experimental studies, which showed that squalene can trigger autoimmunity in animals[86-90]. Although too early for definite conclusions, studies about the safety of vaccines against common seasonal influenza that contain squalene and are in use from 1999 indicate that this immune adjuvant is rather safe for Humans[91,92].

Tuberculosis in hemodialysis

Another respiratory infection with particular characteristics in HD patients is tuberculosis. This mycobacterial infection is a great global health problem since 8 million people develop active tuberculosis annually, 2-3 million die per year and 2-3 billion have latent TB[93]. The emergence of multidrug resistant strains, i.e. to isoniazid and rifampicin, and lately extensively drug resistant strains, i.e. to isoniazid, rifampicin, any fluroquinolone and at least to one of second line injectable drugs (amicacin, kanamycin and capreomycin) alerts the world health community[94-96]. The Bacillus Calmette- Guerin (BCG) vaccine, offers 73% protection from TB meningitis and from miliary TB in children younger than 5 years old. The degree of protection provided by BCG vaccination in adults is controversial and ranges between 0 and 80% in various studies[97-100].

The risk of active TB is increased in HD and often TB is expressed as fever of unknown origin or is located extrapulmonary[101-108]. Due to increased risk of latent TB activation in HD, CDC recommends that patients should be tested with tuberculin skin test (TST). Because of defective cellular immunity in this population, TST is considered positive if the skin induration is larger than 5 mm in diameter. In case of TST positivity preventive treatment with isoniazid alone or in combination with rifampicin is recommended[95,109]. However, in many countries, this policy is limited to renal transplant recipient candidates because of the increased risk of activation after transplantation with detrimental results[110,111]. Unfortunately, TST sensitivity is limited in the HD population because of the increased percentage of anergy (30-40%) to delayed hypersensitivity skin reactions[112-115]. Other methods for diagnosing latent TB like INF-γ release assay (IGRA) or even serologic tests are under research[116,117].

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