Bacteremia and Infection among Hemodialysis Patients

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Conflict of interest: None declared

Funding: No funding sources

Abstract

Infection is a common complication and is the second leading cause of death in hemodialysis patients. The risk of bacteremia in hemodialysis patients is 26-fold higher than in the general population, and 1/2-3/4 of the causative organisms of bacteremia in hemodialysis patients are Gram-positive bacteria. The ratio of resistant bacteria in hemodialysis patients compared to the general population is unclear. Several reports have indicated that hemodialysis patients have a higher risk of methicillin-resistant Staphylococcus aureus infection. The most common site of infection causing bacteremia is internal prostheses; the use of a hemodialysis catheter is the most important risk factor for bacteremia. Although antibiotic lock of hemodialysis catheters and topical antibiotic ointment can reduce catheter-related blood stream infection (CRBSI), their use should be limited to necessary cases because of the emergence of resistant organisms. Systemic antibiotic administration and catheter removal is recommended for treating CRBSI, although a study indicated the advantages of antibiotic lock and guidewire exchange of catheters over systemic antibiotic therapy. An infection control bundle recommended by the Center for Disease Control and Prevention succeeded in reducing bacteremia in hemodialysis patients with either a catheter or arteriovenous fistula. Appropriate infection control can reduce bacteremia in hemodialysis patients.

Keywords: Bacteremia, Infection, hemodialysis patients

Tob Regul Sci.™ 2023;9(1): 5995 - 6003

DOI: doi.org/10.18001/TRS.9.1.418

Introduction

Infection is the second leading cause of death in hemodialysis patients in many countries and is the leading cause of death in the first year of hemodialysis in Japan[1-3]. Furthermore, infection is a major cause of hospitalization in hemodialysis patients. In the United States, infection was observed in approximately 30% of all hospitalizations of hemodialysis patients[4,5]. These data

indicate that infection is a serious threat to these patients. Hemodialysis patients have higher rates of bacteremia, whereas peritoneal dialysis patients have higher rates of peritonitis[4,6]. In a study in the United States, the rates (per 100 person-years) of specific infection-related hospitalizations of hemodialysis patients were 17.6 for septicemia, 15.3 for pulmonary infections, 3.7 for gastrointestinal infections, 12.3 for genitourinary infections, and 10.2 for soft-tissue infections[4]. In a cohort study in Denmark, the incidence of blood stream infection was 13.7 per 100 person-years in hemodialysis patients and 0.53 per 100 person-years in a population control[7]. These data indicate higher risks of bacteremia and a significant need to reduce bacteremia in hemodialysis patients. In this review, we describe the features of bacteremia, including its prevalence, microbiological features, and risk factors in hemodialysis patients. And we describe details of catheter related bacteremia, a characteristic bacteremia in hemodialysis patients. Furthermore we discuss how to reduce the risk of bacteremia in hemodialysis patients.

The incidence of bacteremia in hemodialysis patients is very high compared with its incidence in the general population. A population-based cohort study in Denmark showed that the incidence of bacteremia was 13.7 per 100 person years in hemodialysis patients, whereas that in the general population was 0.53 per 100 person years[7]. The incidence of *Staphylococcus aureus* (*S. aureus*) bacteremia in hemodialysis patients was 46.9-fold that of the general population in Denmark[8]. In studies in Canada, the relative risks of *Pseudomonas aeruginosa* and anaerobe infection were 123.3 and 72.7, respectively, in hemodialysis patients[9,10].

Almost all studies on bacteremia in Japan were case reports[11-13]. Sepsis was the second leading cause of death in infectious diseases in a study in Japan[14]. However, microbiological studies have not been conducted. On the other hand, the greater use of arteriovenous fistula and low catheter use are unique characteristics in Japan[15]. Eighty nine point seven percent of vascular accesses of Japanese hemodialysis patients was native arteriovenous fistula, 7.1% was arteriovenous grafts, 1.8% was superficialization of artery, and only 0.5% was long-term catheters in 2008[16]. It might be a reason why few studies have conducted on catheter related bacteremia in Japan. Further studies are required to clarify about the bacteremia in Japan.

In the Dialysis Outcomes and Practice Patterns Study (DOPPS), adjusted relative risks of mortality were 2.84 for Europe and 3.78 for the United States compared with Japan, although it was speculated because not all dialysis facilities in Japan enrolled in the study[17]. The percentage of infection in cause of death was about 18% in Japan, which is higher than North America and comparable with Europe and Australia/New Zealand in the DOPPS[18]. The other causes of death may contribute to the difference of mortality.

Half to 3/4 of the causative organisms of bacteremia in hemodialysis patients are Gram-positive bacteria 19-21]. The remaining less than 1/4 are Gram-negative. Among the causative organisms, *S. aureus*, including methicillin-resistant *S. aureus* (MRSA), is the most common causative organism. Other staphylococci, including *S. epidermidis* and coagulase negative

staphylococcus (CNS), are also common Gram-positive organisms. *Escherichia coli* (*E. coli*), *Enterobacter* species and *Klebsiella* species are the common Gram-negative organisms isolated from blood samples. The pattern of causative organisms was similar in vascular access-associated and catheter-related bacteremia[20,22]. In hemodialysis patients, rate of *S. aureus* was relatively high and rate of *E. coli* was relatively low compared with the general population[23,24]. It is unclear whether the ratio of resistant bacteria in hemodialysis patients is higher than that in the general population. In a single-center report from Brazil in 2010-2013, 38.5% of *S. aureus* was MRSA[25], whereas the methicillin resistance percentage was 31.0% in surveillance data from Brazil in 2005-2008[26]. However, a national surveillance report for England indicated that the relative risk of MRSA bacteremia was approximately 100-fold higher for dialysis patients than for the general population and was 8-fold higher for patients using a catheter than for those with an arteriovenous fistula[27]. In addition, another surveillance report from the United States also indicated that dialysis patients had a 100-fold higher risk of MRSA infection than the general population[28].

In seven years of hospitalization and death records of hemodialysis patients in the United States Renal Data System, the secondary diagnosis codes among all episodes of septicemia were infection/inflammation caused by internal prostheses (18%), other complications of internal prosthetic device (8%), decubitus ulcer (6%), urinary tract infections (5%), pneumonia (5%), gangrene (3%), endocarditis (2%), and cellulitis and abscess of the foot (1%). These data indicated that septicemia secondary to vascular access infection was the most common cause of septicemia[29]. In the analysis of the causes of hospitalization for infection, the leading causes of hospitalization for infection were dialysis access or central venous catheter-related infections (30%), bloodstream infections or sepsis (24%), and pulmonary infections (22%)[6]. These data also indicated that blood access infection is the most common cause of infection in hemodialysis patients.

The most important risk factor for bacteremia in hemodialysis patients is the use of central venous catheters. Hemodialysis catheter uses were at higher risk of bacteremia compared with arteriovenous fistula or graft uses. A single center study in the United States indicated that the rate of positive blood cultures in patients with central venous catheters was 1.86/1000 d and 0.08/1000 d in patients with an arteriovenous fistula and 0.31/1000 d in patients with an arteriovenous graft[30]. Rate of infection related hospitalization was higher in the patients with catheters or arteriovenous grafts compared with arteriovenous fistula, the rate ratios were 1.59 and 1.37, respectively[5]. Analysis of the United States Renal Data System showed that hemodialysis patients with a temporary catheter had a 50% higher risk of septicemia than patients with a native fistula. Patients with a GOR-TEX or bovine graft had a 33% higher risk of septicemia than patients with a native fistula during throughout seven years of follow-up[29]. In a retrospective study of a hospital in Brazil, a multiple regression analysis showed that the use of a central venous catheter was associated with an 11.2-fold increased risk of bloodstream infections compared with

arteriovenous fistula for vascular access[25]. In addition, a second leading risk factor was previous hospitalizations, which had an odds ratio of 6.63 in a multiple logistic regression analysis[25]. In patient characteristics, the adjusted risk ratios of age > 65 years, diabetes mellitus, and serum albumin < 3.5 were 1.61, 1.26 and 1.66, respectively[29]. The patients who reused dialyzers had a 28% higher risk of septicemia than patients who did not reuse membranes[29].

Long-term catheters are essential for hemodialysis patients whose blood access site is limited. Catheters are a major risk factor for bacteremia as described above, and they cannot be easily changed. Therefore, especially careful handling is needed to prevent catheter-related blood stream infections (CRBSI).

Diagnosis of CRBSI

In the guidelines for the diagnosis and management of intravascular catheter-related infection by the Infectious Diseases Society of America, a definitive diagnosis of CRBSI requires: (1) a set of peripheral blood cultures; (2) blood cultures from a peripheral vein and from a culture of the catheter tip; or (3) cultures from an arterial and venous catheter hub that meet differential time-to-positivity criteria[31]. A report from Canada indicated that blood cultures drawn from a hemodialysis circuit were the most sensitive, specific, and accurate for diagnosing CRBSIs when all culture data and clinical information were factored into the assessment[32]. For the hemodialysis circuit, the values for sensitivity, specificity, and accuracy were 93.5%, 100% and 95%, respectively, whereas peripheral veins had a sensitivity of 93.9%, a specificity of 92.5%, and an accuracy of 93%.

Antibiotic lock for hemodialysis catheter

There are many reports and a meta-analysis of antibiotic lock for hemodialysis catheters[33-39]. The antibiotics include gentamycin, minocycline, cefotaxime, cefazolin, and vancomycin Moreover, antiseptics including taurolidine and trisodium citrate have also been tested. Antibiotic lock therapy significantly reduced CRBSI in all studies. In a subgroup analysis of each antibiotic, the reductions in bacteremia rates remained significant for locks containing gentamicin, minocycline, cefotaxime, and vancomycin and gentamicin, but not for those containing taurolidine, or cefazolin and gentamicin, or citrate[33,39]. Although they are associated with a significant reduction of CRBSI, the guidelines of the Centers for Disease Control and Prevention (CDC) do not recommend the routine use of antibiotic lock, and limit this treatment to patients with long-term catheters who have a history of multiple CRBSIs despite optimal maximal adherence to aseptic techniques because of the potential for side effects, toxicity, allergic reactions, or the emergence of resistance to the antimicrobial agent[40].

Topical antibiotics

The prophylactic effects of the application of topical antibiotics, including mupirocin and polysporin triple antibiotic ointments, to the exit sites of the catheter were also investigated. These

topical antibiotics significantly reduced CRBSI in hemodialysis patients. A randomized trial indicated that the topical use of polysporin triple antibiotic ointment to catheter exit sites reduced the relative risk of bacteremia by 60%, as well as the relative risk of mortality by 78%[41]. Mupirocin ointment is also effective to reduce CRBSI. In a randomized controlled trial, application of mupirocin ointment to the catheter exit sites reduced CRBSI by 85%[42]. However, the rapid emergence of resistant *S. aureus* and CNS has been reported[43-45]. Based on this evidence, the CDC guidelines recommend the antibiotic ointment for only hemodialysis patients.

Antibiotics/antiseptics coated catheters

Antibiotics or antiseptics impregnated or coated catheters can reduce the catheter related bacteremia[46,47]. The duration of catheter use in these studies were within a month, and the efficacy in long term use of these catheter has not been established[48].

Treatment of catheter related bacteremia

Generally, the treatment of bacteremia is the administration of systemic antibiotics and the care of the infection site; for CRBSI, this necessitates catheter removal. Initial treatment is empiric systemic antibiotics and antibiotic lock and 31]. Recommended empirical antibiotics are vancomycin plus empirical gram-negative rod coverage based on local antibiogram data. Catheter removal is required in cases that bacteremia or clinical symptom persists, or in cases that causative organisms could colonize in the surface of catheters For hemodialysis patients, catheters sometimes cannot be removed due to limited blood access sites. Antibiotic lock therapy and guidewire exchange of the catheter are attempted in those cases. A meta-analysis compared systemic antibiotics, antibiotic lock therapy and guidewire exchange of the catheter to treat patients with tunneled hemodialysis catheter-related bacteremia[22]. The cure proportions were significantly higher with antibiotic lock therapy than with systemic antibiotics (OR = 2.08; 95%CI: 1.25-3.45; $P < 0.01$) and were higher with guidewire exchange than with systemic antibiotics (OR = 2.88; 95%CI: 1.82-4.55; $P < 0.001$). In particular, for those with *S. aureus* infections, guidewire exchange achieved a significantly higher cure proportion than both systemic antibiotics and antibiotic lock therapy (OR = 3.33, 95%CI: 1.17-9.46, $P = 0.02$; OR = 4.72, 95%CI: 1.79-12.46, $P = 0.002$). However, guidelines recommend systemic antibiotics and catheter removal, especially for infection with *S. aureus*, *P. aeruginosa*, or *Candida* species[31,48]. Guidewire exchange is considered to be an alternative only if another insertion site is not available. This study described above was a meta-analysis of observational studies. Randomized controlled studies are required to obtain further insight.

In 2009, the CDC established a collaborative project to prevent bloodstream infection in hemodialysis patients[49]. Core interventions included surveillance and feedback using the National Healthcare Safety Network, audits of hand hygiene, observation of vascular access care, and other infection control measures In the analysis of 17 outpatient hemodialysis facilities that participated in the project, in the pre-intervention period, the pooled mean blood stream infections

(BSI) and access-related BSI rates were 1.09 and 0.73 events per 100 patient-months, respectively. After the intervention, these rates decreased to 0.89 and 0.42 events per 100 patient-months, respectively[49]. Furthermore, in a report using positive deviance to improve the infection control measures in addition to the collaborative interventions of the CDC, the incidence of all access-related BSIs reduced from 2.04 per 100 patient-months pre-intervention to 0.75 after employing the collaborative interventions and to 0.24 after augmenting the collaborative interventions with positive deviance[50]. Positive deviance is a behavioral change process based on the observation of those with uncommon, beneficial practices who consequently experience better outcomes than their neighbors who share similar risks[51]. These data indicated that the improvement of infection control practices could reduce bacteremia in hemodialysis patients.

The prevalence of blood stream infection in hemodialysis patients is much higher than in the general population. Furthermore, bacteremia is sometimes life-threatening. Improvement of basic infection control measures, including appropriate hand hygiene, catheter care, and education for medical staff and patients, could reduce the occurrence of bacteremia, although this is difficult because the blood streams of these patients are frequently exposed to extracorporeal devices.

This work following the original work done by Suzuki et al. [52]. Who assessed Bacteremia in hemodialysis patients.

No Conflict of interest.

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