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Potential Risks for and Prognoses After Infections and Antimicrobial use Among Hemodialysis Outpatients: A Prospective Study

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Abstract

Background: The aims of this study were to determine the prevalence and characteristics of infections as well as the use of antimicrobials among hemodialysis outpatients.

Methods: We used the dialysis event surveillance protocol to conduct a prospective study in 2019.

Results: Totally 180 outpatients who received maintenance hemodialysis were included in the cohort study. The total number of dialysis events was 53 in 38 patients. Among the collected events, 42 (79.25%) events used intravenous antimicrobial treatments; five (9.43%) had positive blood cultures; and six (11.32%) had pus, redness, or swelling at the access site. Type of vascular access was an influencing factor for infection among hemodialysis outpatients. Blood flow rate on dialysis was another factor influencing infection events, the risk of infection increased in patients who had lower blood flow rate. Additional analysis showed that lower blood flow rate was also observed as adverse impact in patients who used central lines, but not in those with fistulas. And Erythropoietin use was higher in the infection group.

Conclusions: Patients who used central lines, and especially patients both with central lines and low blood flow rate, were more vulnerable to infection. Using Erythropoietin was another risk factor for infection in hemodialysis outpatients.

Introduction

According to the US Renal Data System 2019 Annual Data Report, the prevalence of end-stage renal disease (ESRD) continues to increase. In 2017, there were 124,500 new cases of registered ESRD, and the prevalence of ESRD reached 746,557 cases in 2017 [1]. In China, the estimated prevalence of hemodialysis use was 402.18 per million, and the number of patients with hemodialysis (HD) has rapidly increased to approximately 553,000 in 2015 [2].

Infections are the second most common cause of hospitalization or mortality after cardiovascular disease in HD patients. Data from the US Renal Data System indicated that the infections accounted for 11% of all mortalities among HD patients[3]. Bloodstream and localized infections of the vascular entry, blood-borne infections such as hepatitis B virus, hepatitis C virus, and HIV; and airborne infections such as tuberculosis are all common infections in HD patients. Contaminated water, equipment, or environmental surfaces present during treatment could be the sources of infections [4]. vascular access for HD carry the infection risks; arteriovenous fistulas, arteriovenous grafts, and central venous catheters (CVCs) could cause the increasing risk of infections [5, 6]. Antibiotics are commonly used to HD patients, which could lead to resistance to the antimicrobial agents and multidrug-resistant organisms. Surveillance of infections and other adverse events among HD patients is useful to strengthen quality improvement and monitor the effectiveness of infection prevention and control measures. In the United States, although CVCs were used for only 19% of HD patients, it was responsible for 69% of access-related bloodstream infections [1]. In addition to access-related

infections, HD patients are also susceptible to non–access-related infections including respiratory infections, urinary tract infections, and skin/soft tissues infections [6, 7]. Therefore, identifying the risk factors for development of infections remains important.

Several studies have used a dialysis event surveillance protocol developed by the National Healthcare Safety Network to describe the prevalence and characteristics of dialysis events and antimicrobial use among HD outpatients[6, 8]. However, many potential risk factors and long-term prognoses were not analyzed. In this study, we conducted a prospective study in our center for 1 year to describe the prevalence and characteristics of HD events, and we aimed to identify potential risk factors for infections.

Materials And Methods

Study design and study participants

This prospective surveillance study was carried out to assess the prevalence and characteristics of dialysis events among HD outpatients in the Second Hospital of Anhui Medical University in 2019. Study participants comprised outpatients who required maintenance HD and excluded inpatients. Maintenance HD was defined as HD lasting at least 3 months in a patient.

During January 2019, our HD unit used standard forms to record participant characteristics (number, age, gender, vascular access type, blood flow, ultrafiltration volume/weight ratio, blood pressure, and therapy year) and collected baseline laboratory data (blood cell count, serum albumin, calcium, phosphate, and parathyroid hormone). We also collected history about specific diseases (i.e., hypertension or diabetes) and some therapies (including the use of erythropoietin, phosphate binder, and activated vitamin D). Dialysis events were collected by questionnaire as they occurred.

Definitions

Three types of dialysis events were reported, as defined by the National Healthcare Safety Network guidelines for dialysis event surveillance: 1) intravenous (IV) antimicrobial treatment initiation; 2) positive blood culture; and 3) pus, redness, or increased swelling at the vascular access site (PRS) [9]. Several additional measures generated from the three dialysis events were also described: 1) access-related bloodstream infection (a bloodstream infection in which the suspected source was vascular access or uncertain); 2) vascular access infection (a PRS, an access-related bloodstream infection, or both); and 3) hospitalization (patients who were hospitalized due to dialysis events). Positive blood cultures and antimicrobial treatment initiation within 1 calendar day after hospital admission were also reported, because outpatients with serious infections were usually admitted to hospital for treatment. The “21-day rule” was applied to reduce the potential for multiple reporting of the same problem [6, 9]. Anemia were defined as hemoglobin levels less than 10 g/dL according to Kidney Disease Improving Global Outcomes(KDIGO) guidelines [10].

Statistical analysis

Dialysis event rates were computed as the total number of events divided by the total number of patient-months, multiplied by 100. Statistical significance in the event rates among the patients with various types of vascular access was compared using the chi-square (χ^2) test. Data analyses were conducted using SPSS software (Version 23.0; SPSS Inc., Chicago, IL, USA). A *P* value of < 0.05 was considered statistically significant.

Results

Overall, 180 outpatients who received maintenance HD in the center were included in the cohort study. Among these participants, the mean age was 57.93 years (SD = 14.61 years), and 75 (41.7%) were women. Among all outpatients, 29.4% were diagnosed with diabetes, and more than three quarters had hypertension. Only 9.44% of patients began dialysis therapy within the past year; approximately 62.22% of outpatients had received HD for more than 3 years. Fistula was the most common type of vascular access (83.33%), followed by tunneled central line (13.33%), nontunneled central line 1.67%), and grafts and others (1.67%) (See Table 1).

During 12 months in 2019, the total number of dialysis events was 53 in 38 outpatients. The data generated an overall pooled three-event rate of 1.70 per 100 patient-months. The patients were divided into two groups according to whether they experienced events or not. The baseline characteristics of the two categories are shown in Table 1. Type of vascular access was an influencing factor for infection among HD patients. Compared with those without infection, patients who experienced at least one event were more likely to use a central line (34.21% vs. 9.86%, *P* = 0.020). We also found that the blood flow rate during dialysis was another influencing factor for infection events (*P* 0.001). Patients who had lower blood flow rate had higher infection risks. Additional analysis showed that the infection incidence rate was equal in different blood velocities in patients who used fistulas (12.50% vs. 2.31%, *P* = 0.712; Figure 1). However, the incidence of infection was higher in patients who used a central line and had a blood flow rate less than 250 mL/min (92.86% vs. 50.00%, *P* = 0.036; Figure 1). The percentage of erythropoietin use was higher in the infection group versus no-infection group, although the mean hemoglobin level was not different. The initial analysis of laboratory data showed that the mean levels were not different across all parameters (See Table 1).

Among documented events, 42 patients (79.25%) were using IV antimicrobials. Additional data showed that the most low respiratory tract infections/pneumonias were the most common reasons for treatment (57.89%). Other infections that required therapy were upper respiratory tract infections (11.32%), gastrointestinal infections (11.32%), urinary tract infections (3.77%), oral infections (3.77%), and some cases without clear focal infection (7.55%). Six cases of PRS (11.32%) and five cases of positive blood cultures (9.43%) were documented (See Table 2). Details about isolated pathogens are shown in Table 3. Seven patients experienced two events during the year, and two people experienced documented events more than three times. There were no differences in any baseline data among these patients. Five people died in the infection group; the incidence of death was higher in this group compared with those who did not experience infections.

We performed a 6-month follow-up survey for patients who experienced infectious events. In the 6 months, two people died, seven people transferred to other units, and four patients refused to take the survey. A total of 25 patients repeated the lab tests at 1 to 2 months and again at 6 months. We found that the neutrophil count was lower after 1 to 2 months and recovered the baseline level after 6 months. The same change was observed in hemoglobin levels. The lymphocyte count continued to increase throughout the 6 months (See Table 4).

Discussion

Surveillance of dialysis events can help identify patient-specific and device-related risks and can promote intervention practices to reduce infections and complications. The pooled three-event rate in the center for this study was similar to overall rates in our region but lower than figures from previous studies in the United States (4.75 per 100 patient-months) [6] and Saudi Arabia (3.1 per 100 patient-months) [11]. We confirmed with this study that infection increased the risk of mortality and that several points were associated with increased risk. First, people who used central lines were more vulnerable to infection events; this outcome was consistent with previous studies [12-14]. Second, blood flow rate was another factor associated with an increasing incidence of infection. The risk of three events was higher in people who had a low blood flow rate during dialysis. Increased blood flow rate can increase urea reduction [15]. A recent study indicated that a rate less than 250 mL/min during HD was associated with higher all-cause mortality in chronic HD patients [16]. Additional analysis showed that there was no difference in patients who used arteriovenous fistulas, regardless of blood flow rate. However, the risk was higher in those who used central lines, especially when combined with a lower blood flow rate. The central line is frequently cited as an independent risk factor for infection, especially bloodstream infection. According to Schwanke et al. [10], 9.1% of patients who used a central line developed a bloodstream infection[12]. One important cause of infection in CVC was the formation of biofilms. These are complex, three-dimensional structures composed of microorganisms living in a microbe-generated extracellular matrix of proteins, nucleic acids, and polysaccharides. They are formed more easily during lower blood flow rates [17-19]. The studies mostly showed a close relationship between biofilms and bloodstream infection . Most events in this study were initiation of IV antimicrobial treatment; the most common reason was not bloodstream infection but respiratory tract infections/pneumonias. No direct evidence showed that biofilms in CVC caused the respiratory tract infections/pneumonias. However, study indicated that biofilms in CVC can lead to bacteremia and persistent inflammatory reactions [20]. Water and uremia toxins are not effectively removed during low blood flow rates. These conditions are all potentially influencing factors that make patients more vulnerable to infections. Therefore, it is important to take effective measures to keep the blood flow rate high in people using CVCs. We also found that those using erythropoietin-stimulating agents (ESA) had more opportunities for infections. Some studies also found that a high ESA dose was an independent predictor for all-cause, cardiovascular, and infectious-related hospitalizations [21, 22]. One nationwide cohort in Japan showed that using ESA, especially long-acting ESA, can increase all-cause death rate. Long-acting ESA use was also associated with an increased rate of infections and malignancies, and increasing risk was positively associated with high-dose of ESA [23].

Therefore, the dose and type of ESA administered to HD patients might be important. Those who need high-dose ESA to reach target of hemoglobin levels should undergo a full evaluation to identify other risk factors for anemia or receive new therapy methods instead of ESA [24].

We compared the levels of serum calcium, phosphate, and parathyroid hormone between the two groups; these were all components connected with renal osteopathy. Activated vitamin D use also was compared. There were no differences in any parameters between the two groups. Although Chronic Kidney Disease - Mineral and Bone Disorder (CKD-MBD) increased the incidence of cardiovascular events, we did not observe the obvious influence on the incidence of infections [25].

We observed the patients in the case group for up to 6 months. We observed that the hemoglobin level and neutrophil count in the infection group decreased after 1-2 months but recovered at 6 months. Notably, the lymphocyte count was keep higher than baseline until the end of follow-up. Lymphocyte count is a very important reflection of the immune system. Circulating blood lymphocytes include populations of T cells, B cells, and natural killer cells. The baseline lymphocyte count was lower in patients with infection events than in those without events, although the difference was not statistically significant. This result might reflect existing immunosuppression in patients who experienced infection events. The baseline increased level remained persistent, potentially reflecting an immune system reaction. However, the clinical influence of this change remains unclear and should be assessed in more detail.

This study has several limitations. The study was conducted in a single center, the population we observed was small, and the events we documented were few; all of these factors may contribute to inaccurate outcomes. Furthermore, analysis of group details between different types of events and classification of the infection severity were difficult because of limited data. Also, we did not observe hygiene and sterilization procedures, which are identified as traditional risk factors for infection. Last, bloodstream infection might have been under-reported, because empiric antibiotic therapy was common.

Conclusion

In summary, this study indicated that infections increased mortality in HD patients. Rates of dialysis events were higher in HD outpatients who had a central line, especially when combined with low blood flow volume. Erythropoietin use also reflected potential increased risk of infections. Influence of HD factors on infection-related events was persistent, so long-term observation of patients is warranted.

Declarations

Ethics approval and consent to participate

All methods in studies involving human participants were inaccordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments. The study protocol was approved by the Ethical Committee of the Second Affiliated

Hospital at Anhui Medical University (The certificate no. PJ-YX2019-007). The informed consent was obtained from all the participantswas and their legal guardian(s) for dead people.

Consent for publication

Not applicable.

Availability of Data and Material

All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

Competing interests

The authors declare that they have no competing interests.

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Not applicable.

Authors' Contributions

Jing-Jing Zhang and Yi-Le Wu designed the study concept. Mei Fang, Wen-Ting Xu, Huai Li and Liang Yuan completed the dialysis event surveillance. JJ Zhang, Xiao-Qian Hu, and Xue-Ping Wang drafted of the manuscript. All authors participated in critical revision of the manuscript for important intellectual content. Jing-Jing Zhang, Yi-Le Wu, and Ruo-Jie Li performed the statistical analysis. Xi-Yao Yang and De-Guang Wang for administrative, technical, and material support.

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Tables

Table 1. Patients’ characteristics at the basline in the hematodialysis Unit.

Characteristic	Run-in Phase (N = 180)	Subgroup		
		With Events (N=38)	Without Events (N=142)	P-Value
Age-Yr	57.93±14.61	61.21±6.27	57.06±14.07	0.120
Female – N(%)	75(41.7%)	19(50%)	56(39.4%)	0.241
Length of therapy duration-Yr	5.23±3.96	5.5±3.95	5.16±3.98	0.640
Hemodialysis blood flow Rate - N(%)*				0.001
200 ml/min	2 (1.08%)	2 (5.3%)	0 (0.00%)	
200-250 ml/min	35(19.44%)	13 (34.21%)	22 (15.49%)	
250ml/min	149(79.58%)	23 (60.53%)	120 (84.51%)	
Ultrafiltration volume/weight ratio- N(%)				0.507
3%	32 (17.78%)	10 (26.32%)	22 (15.49%)	
3%-5%	108 (60.00%)	21 (55.30%)	87 (61.27%)	
5%-7%	35 (19.44%)	6 (15.79%)	29 (20.42%)	
7%	5 (2.78%)	1 (2.63%)	4(2.82%)	
Vascular access type- N(%)*				0.020
Fistula	150(83.33%)	24 (63.16%)	126(88.73%)	
Graft	2 (1.11%)	0 (0.00%)	2 (1.41%)	
Tunneled central line	24 (13.33%)	11 (28.95%)	13 (9.15%)	
Non-tunneled central line	3 (1.67%)	2 (5.26%)	1 (0.70%)	
Other	1 (0.56%)	1 (2.63%)	0 (0.00%)	
With Diabetes- N(%)	53(29.4%)	14(36.8%)	39 (27.5%)	0.260
With hypertension- N(%)	139 (77.2%)	28(73.7%)	111(78.2%)	0.558
Blood pressure — mm Hg				
Systolic	140.21±25.13	138.55±25.01	140.67±25.24	0.646
Diastolic	79.80±12.77	77.92±13.52	80.31±12.57	0.308
Use EPO- N(%)*	137(76.11%)	35(92.11%)	102(71.83%)	0.009
Use iron- N(%)	18(10.16%)	5(13.16%)	13(9.35%)	0.843
Use Phosphate binder- N(%)	71(39.44%)	13(34.21%)	58(40.85%)	0.457

Use vitamin D - N(%)	56(31.11%)	11(28.95%)	45(31.69%)	0.746
WBC-10^9/l	6.14±1.84	6.20±2.49	6.12±1.64	0.847
N-10^9/l	4.22±1.60	4.48±2.33	4.15±1.34	0.411
L-10^9/l	1.30±0.87	1.18±0.86	1.32±0.88	0.344
HB(g/l)	109.54±18.03	107.68±21.68	110.04±16.98	0.476
PLT-10^9/l	170.31±61.45	165.24±50.18	171.67±64.22	0.568
ALB(g/l)	35.85±4.47	35.34±5.31	36.09±4.07	0.462
Ca(umol/l)	2.14±0.31	2.16±0.23	2.14±0.33	0.732
P(umol/l)	1.79±0.57	1.73±0.64	1.82±0.54	0.391
iPTH(pg/ml)	364.99±336.82	496.80±507.63	329.42±265.09	0.071
Death*	11(6.11%)	5(13.16%)	6(4.23%)	0.042

EPO, erythropoietin; WBC, white blood cells; N, neutrophil; L, lymphocyte; HB, hemoglobin; PLT, platelets; ALB, albumin; Ca, calcium; P, phosphate; iPTH, Intact Parathyroid Hormone.

Table 2. Baseline data for patients with hemodialysis events (53C/38P)

Characteristic	No.(%)
Type of events(C)	
Intravenous (IV) antimicrobial start	42(79.25%)
Upper respiratory tract infections	6(11.32%)
Low respiratory tract infections/Pneumonias	22(57.89%)
Gastrointestinal infections	6(11.32%)
Urinary tract infections	2(3.77%)
Oral infections	2(3.77%)
Others	4 (7.55%)
PRS	6(11.32%)
positive blood culture	5(9.43%)
Outcomes(C)	
Hospitalization	40(75.47%)
Death	5(9.43%)
Frequency of event(C/P)	
1	29/29(76.32%)
2	14/7(18.42%)
≥3	8/2(5.26%)

C, cases; P, patients.

Table 3. Difference in isolated pathogens

Pathogens	Whether positive isolated from Catheter	Vascular access type
Escherichia coli	Y	Tunneled central line
Pseudomonas aeruginosa	N	Tunneled central line
Staphylococcus lyonnais	N	Fistula
Staphylococcus epidermidis	Y	Tunneled central line
Lactobacillus brevis	Y	Tunneled central line

Table 4. Patients' characteristics at the follow-up in the hematodialysis Unit.

Characteristic	Baseline	Follow-up for 1-2mon	Follow-up for 6 Mon
WBC-10^9/l	6.08±2.21	5.39±2.26	6.48±1.97
N-10^9/l	4.26±1.88	3.36±1.68*	4.41±1.57
L-10^9/l	1.05±0.47	1.24±0.52*	1.26±0.51#
HB(g/l)	110.20±15.14	101.60±18.41*	109.24±12.56
PLT-10^9/l	153.96±52.29	153.84±68.06	168.72±64.56
Ca(umol/l)	2.23±0.24	2.22±0.22	2.22±0.16
P(umol/l)	1.72±0.62	1.59±0.72	1.59±0.57
iPTH(pg/ml)	473.12±423.32	364.30±322.20	342.18±350.22

WBC, white blood cells; N, neutrophil; L, lymphocyte; HB, hemoglobin; PLT, platelets; ALB, albumin; Ca, calcium; P, phosphate; iPTH, Intact Parathyroid Hormone.

Figures

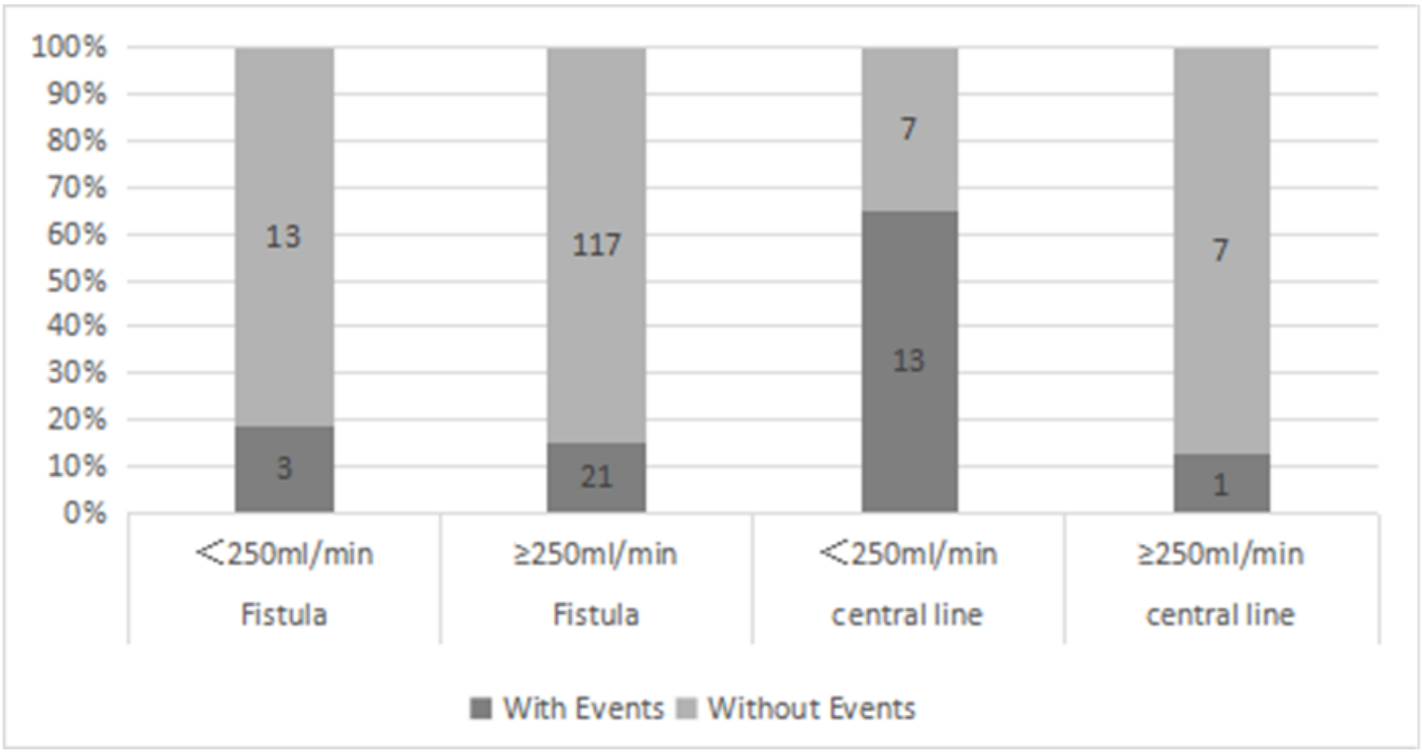

Figure 1

Subgroup for hemodialysis blood flow velocity with different vascular access types