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Original Article

Clinical characteristics, risk factors and microbiology of infections in patients receiving chronic hemodialysis

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ABSTRACT

Background: The infectious complications in hemodialysis patients are still among the main reasons for their increased morbidity and mortality. The possible reasons behind this might be due to impairments in the host defense mechanisms, comorbidities, invasive procedures and pathogenicity of the infecting organisms. With the increased incidence of bacteremia in hemodialysis patients and the overt use of antibiotics, we have witnessed a rise in the number of new multidrug resistant (MDR) strains in those patients.
Aim: We aim to determine the epidemiology, risk factors and complications of infections in patients receiving chronic hemodialysis, particularly bloodstream infections.
Methods: This is a retrospective case-control study involving patients undergoing hemodialysis at a tertiary care center. We studied the prevalence of infectious complications among those patients as well as the responsible agent in each respective infectious episode and the risk factors associated with bacteremia.
Findings: 46.6% of the studied population had at least one documented episode of infection. The most common were blood and respiratory infections (33.2% and 32.7% respectively). Among patients with bacteremia, coagulase-negative Staphylococcus was the predominant pathogen (49% of cases), followed by *Staphylococcus aureus and Escherichia coli*. Mortality was higher in patients who had MDR bacteremia, and in those who had mechanical ventilation or intensive care unit (ICU) admission.
Conclusion: Due to the alarming increase in the incidence of infection among hemodialysis patients and its strong association with mortality, further studies are needed to look for risk factors associated with infection and for ways to control those risk factors.

Introduction

Infectious complications are the second leading cause of morbidity and mortality in dialysis patients after cardiovascular events.[1] The annual mortality secondary to sepsis in dialysis patients is 100- to 300-fold higher compared to the general population.[2] The increased predisposition to infections in these patients is thought to be due to factors associated with impairment of host defenses, such as old age, breach of skin and mucosal barriers, comorbidities, and often malnutrition.[3–5]

Historically, the most common pathogens encountered in hemodialysis patients have been Gram positive cocci, mainly *Staphylococcus aureus* followed by coagulase negative staphylococci.[5,6] However, given the increased use of antibiotics in this particular subset of patients and their recurrent exposure to the healthcare system, there has been a rise in the incidence of infections with multidrug resistant (MDR) organisms. Calfee et al. showed that methicillin-resistant *S. aureus* (MRSA) was the most common among these pathogens, followed by vancomycin-resistant enterococci (VRE) and MDR Gram negative bacilli.[7] However, the proportion of resistant bacteria in hemodialysis patients to those found in the general population is not well elucidated.[8]

Proper identification of locally prevalent pathogens is crucial for providing optimal care for patients since the choice of empiric

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treatment or prophylactic antibiotics prior to planned procedures depends on the prevalent pathogens in a local community. Unfortunately, there is a paucity of such information in the Eastern Mediterranean region, including Lebanon. The purpose of this study is to bridge the gap of information regarding the incidence of infections among hemodialysis patients at the American University of Beirut Medical Center (AUBMC). We intend to identify the risk factors for mortality in bloodstream infections in patients undergoing hemodialysis, with attention to involved organisms and their respective resistance profiles.

Methods

Study design and population

This is a retrospective case control study of patients undergoing chronic hemodialysis at AUBMC between January 2008 and December 2015. AUBMC is a 350-bed tertiary care center that serves as a referral center for Lebanon and the region. All patients aged ≥ 18 years who had been receiving hemodialysis for at least 3 months were included in the study. Patients were included more than once if they developed more than one infection during the period of the study. Data were retrieved by retrospective review of the patients' medical records. Cases consisted of patients who had at least one episode of infection requiring hospitalization, while controls included patients who had never developed an infection requiring hospitalization within the study timeframe. The type of infection with the resistance profile of the isolated organism was recorded and the episodes were classified by the nature of the infection being hospital-acquired or community-onset. The causative organisms in bloodstream infections were classified according to the resistance profile of the pathogen into sensitive or multi-drug resistant (MDR) organisms. MDR organisms were defined according to Magiarakos et al. as being resistant to at least three classes of antibiotics.[9]

Data collection

Demographic characteristics, including age and sex, were collected in addition to the following baseline characteristics: body mass index (BMI), underlying cause of end stage kidney disease (ESKD), age at onset of dialysis, hemodialysis access site, dialysis vintage, and comorbidities. Dialysis vintage was defined as the time (in years) from onset of hemodialysis until acquisition of infection. Detailed information about the episode of infection requiring hospitalization were recorded: place of acquisition, whether hospital or community acquired, antibiotic use prior to admission, Charlson score on admission, duration of hospitalization, need for intensive care unit (ICU) admission, need for mechanical ventilation, and the type of pathogen with its resistance profile. Specific data were collected on bloodstream infections: source of bacteremia, Pitt bacteremia score, complications, and all-cause mortality. An infectious episode was considered hospital-acquired if it manifested 48 h or more after hospital admission or within 7 days of hospital discharge. We defined community-onset infection as one that manifested in a hemodialysis patient who is not hospitalized.

Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) 23 software. Bivariable analysis was performed to test for potential associations using the chi-square test and the independent samples t-test for categorical and continuous variables, respectively. Odds ratios (OR) and their 95% confidence intervals[6] were calculated from 2-by-2 contingency tables. Multivariable logistic regression was used to identify independent predictors of mortality among cases.

Ethical considerations

The study was approved by the American University of Beirut Institutional Review Board.

Results

Population characteristics

A total of 218 patients were enrolled in the study (102 cases and 116 controls). Table 1 summarizes the baseline characteristics of the two groups. Cases were older than controls, with a mean age of 71.1 ± 14.2 vs. 63.8 ± 16.7 years ($p < 0.01$), and had more comorbid conditions, such as coronary artery disease (CAD) [56 (54.9%) vs. 46 (39.6%); $p = 0.05$], congestive heart failure (CHF) [45 (44.1%) vs. 22 (19.0%); $p < 0.01$], and chronic obstructive pulmonary disease (COPD) [19 (18.6%) vs. 6 (5.2%); $p < 0.01$]. They were also less likely to have arteriovenous fistulas as their hemodialysis access and more likely to have tunneled catheters ($p = 0.011$).

Clinical infection

Out of the 218 patients studied, 102 developed at least one infection during the study period, and the total number of infection episodes was 220. Respiratory tract and bloodstream infections accounted for the majority of infectious episodes [73 (33.2%) and 72 (32.7%), respectively]. Urinary infections, skin and soft tissue infections and abdominal infections followed in descending order. Regarding vascular access sites, arteriovenous fistulas were associated with lower rates of bloodstream infections when compared to tunneled and non-tunneled catheters (OR = 0.3; 95% CI 0.2–0.5). However, no significant difference was observed in the rates of bloodstream infections when tunneled catheters were compared to non-tunneled catheters. Table 2 displays the characteristics of infection episodes stratified by whether the infection was classified as hospital acquired or community-onset. Compared with those with community-onset infections, patients with hospital-acquired infections were more likely to have received systemic antibiotics, both within the 24 h [5 (27.8%) vs. 6 (3.0%); $p < 0.01$] and 30 days [9 (50.0%) vs. 58 (28.7%); $p = 0.06$] prior to the onset of infection. They were also more likely to have bloodstream infections, although that difference did not reach statistical significance [9 (50.5%) vs. 63 (31.2%), $p = 0.49$]. The mean duration of hospitalization for hospital-acquired infections was significantly higher (18.5 ± 15.1 vs. 8.6 ± 15.2 days; $p = 0.01$), as was as all-cause mortality (6 (33.3% vs. 23 (11.4%); $p < 0.01$).

Microbiology

Hospital-acquired infections were more likely to be confirmed with positive cultures compared to community-onset infections (77.8 vs. 51.5%; $p = 0.05$) (Table 2). The percentage of MDR organisms among urinary infections was 29.4% (10/34), and all were ESBL-producing Escherichia coli. Respiratory infections were mostly radiologically-diagnosed except in 10 cases where the most common organism was *Pseudomonas aeruginosa* (4/73), followed by *E. coli* ESBL (3/74), *E. coli* (2/74) and *Enterobacter cloacae* (1/73). Among the 72 bloodstream infections, coagulase-negative staphylococci were the predominant pathogens, accounting for 35 (49%) of cases, followed by 11 (15.3%) *S. aureus* and 8 (11.9%) *E. coli*. With regard to staphylococcal isolates, two out of eight *S. aureus* and 22

Table 1
Baseline characteristics of cases and controls.[a]

	Cases (n = 102)	Controls (n = 116)	Unadjusted OR (95% CI)	p-value
Age in years, mean ± SD	71.1 ± 14.2	63.8 ± 16.7		< 0.01
Male gender	64 (62.7)	74 (63.8)	1.0 (0.6–1.7)	0.87
BMI in kg/m^2, mean ± SD	26.7 ± 5.7	30.0 ± 18.0		0.11
Underlying cause of ESKD				
Diabetes mellitus	57 (55.9)	59 (50.9)	1.1 (0.7–1.9)	0.64
Hypertension	91 (89.2)	97 (83.6)	1.3 (0.6–2.9)	0.56
Autosomal dominant polycystic kidney disease	5 (4.9)	1 (0.9)	5.7 (0.7–49.4)	0.78
Glomerulonephritis	6 (5.9)	10 (8.6)	0.6 (0.2–1.8)	0.39
Age at onset of HD in years, mean ± SD	69.8 ± 15.4	62.0 ± 17.1		0.01
Access site for HD				0.011
AV fistula	54 (52.9)	81 (69.8)		
Tunneled catheter	40 (39.2)	24 (20.7)		
Non-tunneled catheter	8 (7.8)	11 (9.5)		
Co-morbidities				
Coronary artery disease	56 (54.9)	46 (39.6)	1.7 (1.1–3.0)	0.05
Congestive heart failure	45 (44.1)	22 (19.0)	3.2 (1.7–5.9)	< 0.01
Peripheral vascular disease	40 (39.2)	42 (36.2)	1.1 (0.6–1.8)	0.84
COPD	19 (18.6)	6 (5.2)	4.0 (1.5–10.6)	< 0.01

OR = odds ratio; CI = confidence interval; SD = standard deviation; BMI = body mass index; ESKD = end stage kidney disease; HD = hemodialysis; AV = arteriovenous; COPD = chronic obstructive pulmonary disease.
[a] All numbers indicate no. (%) unless otherwise specified.

Table 2
Characteristics of infection episodes by place of acquisition of the infection.[a]

	Hospital-acquired (n = 18)	Community-onset (n = 202)	p-value
Antibiotic use within 24 h	5 (27.8)	6 (3.0)	<0.01
Antibiotic use within 30 d	9 (50.0)	58 (28.7)	0.06
Time from onset of infection to discharge in days	18.5 ± 15.1	8.6 ± 15.2	0.01
Charlson Comorbidity Index	5.9 ± 2.1	5.5 ± 2.0	0.45
Site of infection			0.49
Bloodstream	9 (50.0)	63 (31.2)	
Respiratory tract	5 (27.8)	68 (33.7)	
Skin and soft tissue	2 (11.1)	20 (9.9)	
Urinary tract	1 (5.6)	33 (16.3)	
Abdominal	1 (5.6)	18 (8.9)	
Microbiology			
Positive cultures	14 (77.8)	104 (51.5)	0.05
CoNS	5/14 (35.7)	42/104 (40.4)	0.74
S. aureus	1/14 (7.1)	11/104 (10.6)	1.0
Enterococcus spp.	0	3/104 (2.9)	1.0
E. coli	5/14 (35.7)	23/104 (22.1)	0.26
Other GNR	3/14 (21.4)	25/104 (24.0)	1.0
MDR organism	3/14 (21.4)	34/104 (32.7)	0.54
Access site for HD			0.72
AV fistula	11 (61.1)	118 (58.4)	
Tunneled catheter	5 (27.8)	70 (34.6)	
Non-tunneled catheter	2 (11.1)	14 (6.9)	
Complications[b]	11 (61.1)	114 (56.4)	0.70
All-cause mortality	6 (33.3)	23 (11.4)	<0.01

OR = odds ratio; CI = confidence interval; SD = standard deviation; CoNS = coagulase-negative staphylococci; GNR = Gram-negative rods; HD = hemodialysis; AV = arteriovenous.
[a] All numbers indicate no. (%) or mean ± SD unless otherwise specified.
[b] Complications include cardiac arrest, prolonged hospital stays, hospital-acquired pneumonia, sepsis, urinary tract infection, and hospital readmission.

out of the 27 coagulase-negative staphylococci were methicillin-resistant. Among clinical specimens yielding positive cultures, MDR pathogens contributed to 37 (31.4%) episodes, and the prevalence of MDR pathogens was not different between hospital-acquired infections vs. community-onset infections (Tables 2 and 3). In particular, there were six cases of endocarditis among bloodstream infections, with no significant difference between sensitive (n = 2) and MDR organisms (n = 4) as etiologic pathogens. Upon examining the distribution of clinical variables according to antimicrobial susceptibility among bloodstream infections, we found that mortality was significantly higher in the setting of infections with MDR organisms compared to susceptible organisms [6 (30.0%) vs. 3 (8.8%); p = 0.04].

In-hospital mortality

When assessing for predictors of mortality for all infectious episodes (Table 4), we found that, on bivariable analysis, mortality was higher in the setting of mechanical ventilation (OR = 28.1), ICU admission (OR = 12.4), and any complication (OR = 5.7). Among the comorbidities, only peripheral vascular disease was considered a risk factor associated with 2.4 times higher odds of death (p = 0.03). After adjusting for complications and risk factors, only mechanical ventilation was significantly associated with mortality (adjusted OR = 17.8; 95% CI 3.6–88.6). Of note is that there was no difference in mortality between patients who developed a single infection compared to those who developed multiple infections (p = 0.169).

Table 3
Comparison of clinical findings between bloodstream infections caused by antibiotic-susceptible and multi-drug resistant organisms.[a]

	MDR organism (n = 20)	Susceptible organism (n = 34)	Unadjusted OR (95% CI)	p-value
Admission to ICU	4 (20.0)	7 (20.6)	1.0 (0.2–3.8)	0.96
Mechanical ventilation	3 (15.0)	2 (5.9)	2.8 (0.4–18.6)	0.26
Complications	15 (75.0)	23 (67.6)	1.4 (0.4–5.0)	0.57
Pitt bacteremia score	1.6 ± 1.8	2.0 ± 2.1	0.9 (0.7–1.2)	0.56
Access site				0.23
AV fistula	10 (50.0)	10 (29.4)		
Tunneled catheter	7 (35.0)	20 (58.8)		
Non-tunneled catheter	3 (15.0)	4 (11.8)		
Site of acquisition			5.8 (0.6–60.3)	0.12
Hospital-acquired	3 (15.0)	1 (2.9)		
Community-onset	17 (85.0)	33 (97.1)		
All-cause mortality	6 (30.0)	3 (8.8)	4.4 (1.0–20.3)	0.04

MDR = multi-drug resistant; OR = odds ratio; CI = confidence interval; ICU = intensive care unit; AV = arteriovenous.
[a] All numbers indicate no. (%) unless otherwise specified.

Table 4
Bivariable and multivariable analysis of risk factors for in-hospital mortality for all infectious episodes.

	Lethal infection (n = 29)	Non-lethal infection (n = 191)	Unadjusted OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
PVD	18 (62.1)	77 (40.3)	2.4 (1.1-5.4)	0.03	2.4 (0.8–7.0)	0.10
Hypertension	28 (96.5)	176 (92.1)	2.4 (0.3-18.8)	0.40	2.7 (0.2–38.1)	0.46
CHF	20 (69.0)	99 (51.8)	2.1(0.9-4.8)	0.08	1.7 (0.6–5.0)	0.35
BSI	13 (44.8)	59 (30.9)	1.8 (0.8-4.0)	0.14	2.3 (0.8–6.9)	0.14
Complications	25 (86.2)	100 (52.4)	5.7 (1.9-17.0)	< 0.001	2.4 (0.7–8.5)	0.14
ICU admission	20 (69.0)	29 (15.2)	12.4 (5.2-30.0)	< 0.001	2.0 (0.5–7.8)	0.32
MV	16 (55.2)	8 (4.2)	28.1 (10.2-78.0)	< 0.001	17.8 (3.6–88.6)	<0.001

OR = odds ratio; CI = confidence interval; PVD = peripheral vascular disease; CHF = congestive heart failure; BSI = bloodstream infection; ICU = intensive care unit; MV = mechanical ventilation.

Discussion

This retrospective study is the first from Lebanon to systematically evaluate infection episodes among patients receiving hemodialysis and to examine predictors of mortality in this patient population. In 2015, a non-comparative report from our center described a cohort of patients on hemodialysis presenting to the Emergency Department with sepsis.[10] The dialysis catheter was deemed to be the most common source of infection (26.7%), followed by respiratory (15.6%) and urinary tracts (11.1%). Among causative organisms, there was a predominance of *E. coli* (24.4%) followed by coagulase negative staphylococci (22.2%). *S. aureus* accounted for only 5.6% of cases. The investigators found that the mortality rate was 26.6% during the index hospitalization.

In our study, the 218 patients studied contributed a total of 569 years of hemodialysis and developed 220 infections requiring hospitalization during the study period. This yields an infection incidence density of 125.2/1,000 dialysis-years. To our knowledge, the measurement of "infection incidence density" per dialysis-years is not used. However, we believe that it is an important factor to be reported in such studies, because it will take into consideration the time at risk, similar to the reporting of device-associated infections using device-days.

Not surprisingly, cases were older than controls and had more comorbidities such as CAD, CHF, and COPD. Previously published data has established that bacteremia is the most common form of severe infection in dialysis patients.[8,11] Consistent with the available evidence, arteriovenous fistulas were associated with fewer bloodstream infections compared to tunneled and non-tunneled catheters.[12,13] However, this study was not able to show a statistically significant difference between the incidence of infections with both types of catheters.[12,14] The number of patients who had a non-tunneled catheter compared to other access sites was low. This reflects that at our institution, there is limited use of the non-tunneled catheters due to the higher risk of infection associated with their use compared to the tunneled catheters.

The overall prevalence of MDR pathogens among infected hemodialysis patients was high, reaching 31.4%. This indicates the need for the initiation of broad empirical antimicrobial coverage, taking into consideration the local resistance patterns, which should be followed by prompt de-escalation as soon as cultures become available. Broad empirical therapy is especially important in patients suspected of having bloodstream infections, where we showed that infections with MDR pathogens are associated with higher mortality. Since we found that patients with community-onset infections have a better outcome, these patients would be particularly suitable candidates for rapid de-escalation once an MDR infection is excluded. Furthermore, and although there was no statistically significant difference in the resistance profiles between hospital-acquired and community-onset infections, this did not translate into similar clinical outcomes. Indeed, patients who acquired their infection while hospitalized fared worse than those who were not hospitalized at the time of infection, with a statistically significant difference in the length of stay (18.5 ± 15.1 vs. 8.6 ± 15.2; p = 0.01) and mortality (33.3% vs. 11.4%; p < 0.01). This might have been driven by the fact that hospitalized patients have a more compromised immune status and are at risk for multiple and recurrent infections, as evidenced by a sizable, albeit not statistically significant, increased likelihood of antibiotic use within the 30 days preceding the infection (50.0% vs. 28.7%; p = 0.06).

In a retrospective study by Berman et al., the most common bloodstream pathogens encountered in hemodialysis patients were coagulase negative staphylococci followed by *S. aureus*.[15] Another study conducted by Fram et al. showed that methicillin-resistant *S. aureus* (MRSA) was the most common resistant pathogen responsible for bacteremia in hemodialysis patients, which was associated with increased morbidity and mortality.[16] Data from the Middle East region on the microbiology of infections in hemodialysis is scarce. However, a prospective study done at King Fahed hospital

in Saudi Arabia showed that the most common pathogens causing bacteremia in hemodialysis patients were *Staphylococcus* species, with the majority being *Staphylococcus epidermidis*, followed by gram-negative organisms.[17] We also found a preponderance of coagulase-negative staphylococci and *S. aureus*, followed by *E. coli* as the third most common bloodstream pathogen. The relatively high frequency of *E. coli* has been previously shown in two articles published in the United States and Spain, both showing an increased proportion of catheter-related bacteremia caused by Gram-negative organisms.[18,19] This has implications on the choice of empiric therapy in the hemodialysis patient presenting with a suspected bacteremia, calling for the addition of Gram-negative coverage to the initial regimen that usually consists of a glycopeptide. The study by Berman et al. illustrated that cefazolin was the most commonly used antibiotic in ESKD patients.[15] Our study assessed antibiotic use in bacteremic patients and found that glycopeptides were most commonly used, followed by meropenem and piperacillin/tazobactam. This may be attributed to elevated local resistance rates among Gram-negative bacilli, namely a high prevalence of extended-spectrum beta-lactamase (ESBL) producing organisms.[20]

We found that 33.9% of bloodstream infections were caused by MDR organisms. This result is better than what was reported in a recent study done at an Algerian hospital, where all organisms incriminated in hemodialysis catheter-related infections were multi-drug resistant, a result that was attributed to poor compliance with hand hygiene.[21] Current literature clearly associates MDR organisms with increased morbidity and mortality.[22] In our study, MDR pathogens causing bloodstream infections were associated with a higher risk for mechanical ventilation and a slightly higher risk of complications compared to susceptible organisms, although these differences did not reach statistical significance, due to the small numbers in each group. Contrary to expectations, using the Pitt bacteremia score was not helpful in our study to predict mortality in the MDR and susceptible organism groups.[23,24] Despite similar mean Pitt bacteremia scores in both arms, all-cause mortality was markedly higher in patients infected with MDR organisms (30.0% vs. 8.8%; OR 4.4, 95% CI 1.0–20.3; p = 0.04). This highlights the importance of understanding the limitations of clinical scoring systems and their applicability to specific patient populations, in this case the hemodialysis population.

Peripheral vascular disease was shown, on bivariable analysis only, to negatively impact survival in infected patients. The effect of vascular disease on infected ESKD patients has not been clearly illustrated in existing literature. However, peripheral vascular disease has been shown to be a risk factor for sepsis in a study conducted by Wang et al.[25] A study by Spronk et al. supported the idea that sepsis with organ dysfunction is a microcirculatory impairment. As such, one would hypothesize that peripheral and especially microvascular disease may exacerbate the circulatory impairment associated with severe sepsis.[26] The development of complications and ICU admission were two more risk factors that were predictive of mortality on bivariable analysis. After controlling for confounders, only the need for mechanical ventilation was independently and substantially associated with a lethal infection, with an increased risk of death by almost 18-fold.

The limitations of this study include being from a single center. However, AUBMC is an advanced, high volume center, which serves a large proportion of Lebanon and the region's diverse population. Moreover, many of the non-bloodstream infections were diagnosed clinically. As such, the microbiology of these infections could not be studied in great detail.

Conclusions

This study is the first to describe the epidemiology of infections in dialysis patients in Lebanon. It showed a predominance of respiratory and bloodstream infections, and a high risk of mortality in patients with hospital-acquired infections, particularly if they require mechanical ventilation. We hope these results invite additional studies to explore a wider spectrum of risk factors and a larger population.

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Competing interests

None declared.

Ethical approval

Not required.

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