Abstract

Introduction: Hemodialysis patients are at risk of infections. This study examines the spectrum of infections and antibiotic resistance patterns. Methods: We retrospectively reviewed the records of 586 hemodialysis patients from May 2018 to April 2020 in a tertiary care hospital in North India. Results: The study identified 99 episodes of confirmed infections. Urinary tract infections were the most common type of infections (55.5%), followed by catheter-related bloodstream infections (CRBSI) (definitive 21.2%). Other infections were pneumonia (8.1%), tuberculosis (6.1%), skin and soft tissue infection (4.0%), dengue fever (3.03%), and empyema thoracis (1.0%). Overall, Escherichia coli (33.3%) was the most common organism isolated. The most frequent uropathogens recovered were *Escherichia coli* (54%). In confirmed CRBSI, *P. aeruginosa* (23.8%) and MSSA (23.8%) were the most common pathogen isolated. K. pneumonia (37.5%) was the most common pathogen in pneumonia. Uropathogens showed the highest resistance to fluoroquinolones (93.3%-100%). Pathogens isolated in CRBSI showed maximum resistance to ciprofloxacin (100%). In pneumonia, the highest resistance was seen to third-generation cephalosporins (75%-100%). Conclusion: Though the bacterial spectrum remains the same over time, antibiotic resistance is changing in uropathogens. There is a trend of predominance of Gram-negative bacterial infections in CRBSI. Tuberculosis incidence rate was much higher than the general population. There is a need for nationwide and worldwide continuous surveillance.

Keywords: Antibiotic resistance, catheter-related bloodstream infection, chronic kidney disease, CRBSI, hemodialysis

Introduction

Infection is the second leading cause of death in patients on hemodialysis (HD).^[1] HD patients visit emergency medical services around six times more often than their age-matched general populations, and infection is the second most common reason for hospitalization in this population.^[2,3] Chronic kidney disease patients on HD are vulnerable to not only catheter-related bloodstream infections (CRBSI) but also to other types of infection. This subgroup of patients is at risk of infections due to malnourishment, impaired immunity secondary to renal failure, comorbidities, and breakdown of anatomical barriers due to repeated intravascular intervention Though for hemodialysis.^[4-6] there are few recent Indian studies^[7,8] on

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access-related infections, literature on non-access-related infections is scarce in HD populations. The aim of this study is to determine the spectrum of infections and the causative pathogens with their antibiotic resistance pattern in HD patients. Bacterial spectra and antibiotic susceptibility patterns vary geographically. The knowledge of infection epidemiology and antibiotic resistance patterns is necessary to choose optimal empirical treatment in such patients.

Material and Methods

Study design

Retrospective study of patients undergoing hemodialysis at the Department of Nephrology, AIIMS Jodhpur, Rajasthan, India over a 2-year period (May 2018–April 2020).

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Eligibility criteria

Eligible subjects were patients on hemodialysis who had symptomatic, microbiologically confirmed infection. We excluded patients less than 18 years. For CRBSI definition (definitive and probable), the KDOQI guideline was used.^[9] For urinary tract infection (UTI) case definition, symptomatic with urine culture showing growth of $\geq 10^5$ colony-forming units/mL was used. For pneumonia, clinico-radiological evidence with isolation of infective organism from sputum or bronchial aspirate was used.

Data collection

Hospital electronic data records including patient discharge summaries were accessed for data collection. Culture and sensitivity reports of blood, urine, and other normally sterile body fluids were collected. Approval from the institute's ethical committee was obtained.

Statistical analysis

Incidence of various types of infection rates was calculated. Definitive CRBSI rate was calculated per 1000 catheter days of hemodialysis. The number of catheter days was obtained by multiplying the average number of patients with catheters undergoing dialysis every year in the unit with the number of days in that calendar year. Incidence rate of pneumonia was expressed per 100 patient-years. Tuberculosis incidence was expressed per 100,000 patients per year. Descriptive statistics were used for data analysis, and the results were expressed in frequency or percentage. Statistical analysis was done using SPSS version 25 (Statistical Packages for the Social Sciences, Chicago, IL).

Results

Patient characteristics

The medical records of 586 patients requiring long-term hemodialysis between May 2018 and April 2020 were reviewed. There were 4967 dialysis days and 109,294 catheter days. In total, 99 microbiologically confirmed infective episodes occurred. The infective episodes occurred in 77 male (77.8%) and 22 female (22.2%) patients. Their median age was 40 years (20–80). Ninety-three (93.9%) out of 99 patients had only one infective episode, five (5.05%) had two, and one (1.01%) had three infective episodes.

Clinical infections

A total of 99 infective episodes were identified. Fever, chills, breathlessness, cough, urinary tract symptoms, and hypotension were the common presenting symptoms. UTIs were the most common type of infections (55.5%, n = 50). CRBSI was the second most common type of infection (confirmed: 21.2%, n = 21; probable: 6.1%, n = 6), followed by community acquired pneumonia (8.1%, n = 8). Tuberculosis (TB) was detected in 6.1% (n = 6),

including four pulmonary TB, one bone TB, and one TB lymphadenitis. Other infections identified included skin and soft tissue infection (SSTI) in 4.04% (n = 4), dengue fever in 3.03% (n = 3), and empyema thoracis in 1.01% (n = 1).

Microbiology

Overall, Escherichia coli (33.3%) was the most common organism isolated, followed by Klebsiella pneumoniae and Pseudomonas aeruginosa (12.1% each). Gram-negative bacteria (GNB) were the most common isolate in UTI. The most frequent uropathogens recovered were Escherichia coli (54%, n = 27), K. pneumoniae (10%, n = 5), *P. aeruginosa* (10%, n = 5), and *Enterobacter* spp (10%, n = 5). In confirmed CRBSI, GNB accounts for 71.4% of the pathogen isolated, and the remaining 28.6% is made of up Gram-positive bacteria (GPB) such as Methicillin-sensitive Staphylococcus aureus (MSSA) and Enterococcus faecalis. Both P. aeruginosa (23.8%, n = 5) and MSSA (23.8%, n = 5) were the most common pathogen isolated. In community-acquired pneumonia, GNB were more common than GPB (87.5% vs. 12.5%), and K. pneumonia (37.5%, n = 3) was the most common respiratory pathogen, followed by Acinetobacter baumanii (25%, n = 2). Mycobacterium tuberculosis (MTB) was identified in six patients (6.1% of all the infections). SSTI was caused by MSSA (50%, n = 2), E. coli (25%, n = 1), and K. pneumonia (25%, n = 1). MSSA was isolated from one patient with empyema. Details of the microbiological profile are shown in Table 1.

Antibiotic susceptibility pattern

Uropathogens showed the highest resistance to fluoroquinolones (93.3%–100%), ceftriaxone (83.3%), and ampicillin (79.3%). Details of the antibiotic susceptibility in UTI are shown in Table 2 and Figure 1. Pathogens isolated in CRBSI showed maximum resistance to ciprofloxacin (100%), ceftriaxone (77.7%), and cotrimoxazole (66.6%), as shown in



Figure 1: Overall antibiotic resistance pattern in urinary tract infection

Table 3 and Figure 2. In pneumonia, the highest resistance was seen to third-generation cephalosporins (75%-100%), cotrimoxazole (75%), and fluoroquinolones (66.6%); the complete spectrum is given in Table 4 and Figure 3. In SSTI, MSSA showed resistance to penicillin G (50%) and



full susceptibility to erythromycin, clindamycin, and levofloxacin; *K. pneumonia and E. coli* were resistant to all the antibiotics tested (penicillin G, piperacillin-tazobactam, ceftriaxone, cefepime, gentamicin, cotrimoxazole, and meropenem), with the exception of tigecycline and colistin. MSSA isolated from empyema did not show resistance to any of the drugs tested.



Figure 2: Overall antibiotic resistance pattern in CRBSI

Figure 3: Overall antibiotic resistance pattern in Pneumonia

Table 1: Microbiological spectrum in different clinical infections										
Pathogen	Types of infections									
	UTI n (%)	CRBSI n (%)	Pneumonia <i>n</i> (%)	SSTI <i>n</i> (%)	Empyema n (%)					
Escherichia coli	27 (54)	3 (14.3)	-	1 (25)	-					
Klebsiella pneumoniae	5 (10)	3 (14.3)	3 (37.5)	1 (25)	-					
Pseudomonas aeruginosa	5 (10)	5 (23.8)	1 (12.5)	-	-					
Enterobacter sp.	5 (10)	1 (4.8)	1 (12.5)	-	-					
Enterococcus faecalis	4 (8)	1 (4.8)	-	-	-					
Burkholderia capacia	2 (4)	1 (4.8)	-	-	-					
Acinetobacter baumanii	1 (2)	2 (9.5)	2 (25)	-	-					
CONS	1 (2)	-	-	-	-					
MRSA	-	-	1 (12.5)	-	-					
MSSA	-	5 (23.8)	-	2 (50)	1 (100)					

CONS: Coagulase-negative staphylococcus, MRSA: Methicillin-resistant Staphylococcus aureus, MSSA: Methicillin-sensitive Staphylococcus aureus

Table 2: Antibiotic resistance for UTIs															
Pathogens	Antibiotic resistance (% resistance)														
	AP	РТ	СТ	СХ	GN	AK	СР	LE	NX	со	NT	MP	IP	EP	AZ
E. coli ⁺	88.8	53.8	50	91.3	28	30	100	100	100	58.3	4	11.1	50	25	100
K. pneumoniae‡	100	50	100	80	50	66.6	50	-	100	80	60	66.6	100	100	100
P. aeruginosa	-	-	0	80	50	-	100	0	100	-	-	0	33.3	-	0
Enterobacter	100	0	0	0	66.6	-	-	0	100	0	100	0	0	0	0
E. faecalis§	33.3	-	-	-	50	-	100	-	-	-	33.3	-	-	-	-
B. capacia	-	0	0	-	-	100	100	100	-	0	0	100	-	-	-
A. baumanii	0	0	0	0	0	-	100	0	-	100	-	-	-	-	-
CONS [¶]	-	-	0	-	100	-	100	-	-	100	-	-	-	-	-
Overall resistance	79.3	26.4	23	83.3	51.4	31.3	93.3	93.3	100	58.8	20	25	37.5	28.5	25

AM: Ampicillin, PT: Piperacillin-tazobactam, CT: Ceftazidime-tazobactam, CX: Ceftriaxone, GN: Gentamicin, AK: Amikacin, CP: Ciprofloxacin, LE: Levofloxacin, NX: Norfloxacin, CO: Cotrimoxazole, NT: Nitrofurantoin, MP: Meropenem, IP: Imipenem, EP: Ertapenem, AZ: Aztreonam, † & ‡: No resistance to Fosfomycin, § & ¶: No resistance to Vancomycin

Table 3: Antibiotic resistance pattern for CRBSI														
Pathogens	Antibiotic resistance (% resistance)													
	РТ	СТ	СХ	CZ	GN	AK	СР	LE	со	MP	IP	EP	AZ	ТР
S. aureus (MSSA) ⁺	-	-	-	-	0	-	100	100	80	-	-	-	-	66.6
P. aeruginosa	25	0	-	-	60	40	100	0	-	75	50	-	60	-
K. pneumoniae	33.3	100	66.6	33.3	50	50	-	66.6	-	33.3	0	50	50	-
E. coli	66.6	50	100	-	66.6	33.3	100	-	66.6	66.6	-	50	100	-
A. baumanii [‡]	-	-	100	-	-	50	100	-	-	50	-	-	-	-
E. faecalis§	-	-	-	-	0	0	-	0	-	-	-	-	-	0
B. capacia	-	0	-	-	0	-	-	0	100	0	-	-	-	-
Enterobacter	-	0	0	-	0	0	-	-	100	0	0	0	0	-
Overall resistance	33.3	28.5	77.7	20	33.3	38.4	100	30.7	66.6	50	33.3	40	63.4	50

PT: Piperacillin-tazobactam, CT: Ceftazidime, CX: Ceftriaxone, CP: Cefoperazone, GN: Gentamicin, AK: Amikacin, CP: Ciprofloxacin, LE: Levofloxacin, CO: Cotrimoxazole, MP: Meropenem, IP: Imipenem, EP: Ertapenem, AZ: Aztreonam, TP: Teicoplanin, † & §: no resistance to Vancomycin and Linezolid, ‡: No resistance to Colistin

Table 4: Antibiotic resistance pattern for pneumonia													
Pathogens	Antibiotic resistance (% resistance)												
	РТ	СТ	СХ	CF	CZ	GN	СР	LE	со	MP	AZ		
S. aureus (MRSA)	-	-	-	-	-	0	-	100	0	-	-		
P. aeruginosa	0	0	-	0	-	0	0	-	-	-	0		
K. pneumoniae	66.6	100	100	100	50	66.6	100	50	100	66.6	100		
A. baumanii	100	100	100	100	100	100	100	100	100	100	-		
Enterobacter	0	-	100	100	0	0	-	0	0	0	-		
Overall resistance	57.1	75	100	85.7	100	50	66.6	66.6	75	66.6	50		

PT: Piperacillin-tazobactam, CT: Ceftazidime, CX: Ceftriaxone, CF: Cefepime, CZ: Cefoperazone, GN: Gentamicin, AK: Amikacin,

CP: Ciprofloxacin, LE: Levofloxacin, CO: Cotrimoxazole, MP: Meropenem, AZ: Aztreonam

Discussion

The study was done to retrospectively analyze the spectrum of confirmed infective episodes and antibiotic resistance patterns, and it was not designed to show risk factors or outcomes. Data were compiled from the institute's hospital information system where all the patients' clinical, radiological, and laboratory data are stored.

The study included 4,967 dialysis days, 109,294 catheter days, and there were 99 episodes of confirmed infection requiring therapeutic intervention. The overall infection rate was 19.9 episodes per 1000 days of dialysis, which was much higher than the 5.7 per 1000 days of dialysis reported by Berman *et al.*^[10]

UTI in hemodialysis patients is less well studied, the literature is scarce, and the exact incidence remains unknown in this group of patients. D'Agata *et al.*^[11] reported that UTIs were the most common nosocomial infections among chronic hemodialysis populations, accounting for 47% of all the infections. They also found that UTIs were more common among the chronic hemodialysis populations (4.2/1,000 patient-days) compared with patients not receiving hemodialysis (0.7/1,000 patient-days). Among hemodialysis patients, *enterococci* and *Candida spp* were the most common organisms in contrast to

Staphylococcus aureus and coagulase-negative staphylococci among patients not on hemodialysis. They did not include community-acquired infections in the study. In our study, both communities acquired and hospital-acquired infections were included. UTIs were the most common infections, accounting for 55.5% of all the infections noted. In contrast to the previous study, Gram-negative bacteria were the most common pathogen (90% of all the UTIs, 54% of those E. coli). Considering frequent contamination or colonization, we excluded Candida spp isolated from urine specimens in our study. The bacterial spectrum causing UTIs remains the same compared to reports from the Indian general population.^[12,13] There was high overall antibiotic resistance to ampicillin, ceftriaxone, fluoroquinolones, aminoglycosides, and cotrimoxazole. Compared to other Indian studies in general populations, we noted a higher level of overall antibiotic resistance to fluoroquinolones and carbapenems.^[13] Considerable susceptibility still retained piperacillin-tazobactam, ceftazidime-tazobactam, to carbapenems, aztreonam, nitrofurantoin, and fosfomycin.

There has been a significant decline in the incidence of CRBSI over the past decade across the globe. During the study period, there were 21 definitive CRBSI episodes, of which 17 (80.95%) occurred in temporary catheters and four (19.05%) in permanent tunneled catheters, and six episodes of probable CRBSI. The overall incidence rate was 0.24 per 1000

catheter-days (definitive: 0.19/1000, probable: 0.054/1000), which is lower than that in older studies (5.3-6.5/1000 catheter-days).^[14-16] However, our finding is comparable to a recent Indian study (0.2/1000 catheter-days) and a recent study from Alberta, Canada (0.19/1000 catheter-days).^[7,17] While reports from developed countries consistently showed the predominance of Gram-positive bacteria (GPB),^[18,19] recent reports from the developing world showed a trend of Gram-negative bacteria (GNB) predominance.^[8,20] In our study, GNB accounts for 71.4% of the pathogen isolated, and the remaining 28.6% is made of up GPB such as S. aureus (MSSA) and E. faecalis. Both P. aeruginosa and S. aureus (MSSA) were the most common pathogen isolated (23.8% each), which is similar to Gupta et al.^[8] report of P. aeruginosa predominance, and Shah et al.^[7] report of S. aureus (MSSA) predominance. S. aureus showed high resistance to fluoroquinolones and cotrimoxazole, but no resistance to vancomycin or linezolid. P. aeruginosa showed high resistance to ciprofloxacin (100%), meropenem (75%), gentamicin (60%), and aztreonam (60%); lower resistance to piperacillin-tazobactam (25%) and amikacin (40%); and no resistance to levofloxacin. B. capacia and Enterobacter showed resistance only to cotrimoxazole. No drug resistance was noted in E. faecalis. Based on this study, it is still advisable to use empirical GPB and GNB coverage with vancomycin plus aminoglycoside for CRBSI episodes in this part of India. However, each institution should have its own data and recommendation.

It is surprising that pneumonia and the causative organisms in dialysis patients have received relatively less research attention. Estimated mortality rates from pneumonia in dialysis populations are 14–16 times more than in the general population.^[21] Guo et al.^[22] reported pneumonia incidence of 27.9/100 patient-years in the hemodialysis population. A subsequent observational study in the dialysis population found a pneumonia incidence of 21.4/100 patient-years, 30-day mortality of 10.7%, and that 90.1% required hospitalization.^[23] Berman et al.^[10] found that pneumonia contributed 13% of all infective episodes in patients on long-term dialysis. In our study, pneumonia contributed to 8.1% of the infective episodes, and the incidence of pneumonia was 0.68/100 patient-years, which is much lower than that noted in previous studies. The incidence of pneumonia per 1000 person-years in our study (13.6/1000 person-years) was comparable to the estimated incidence in the general population (1.5–14/1000 person-years).^[24] The lower incidence of pneumonia in our analysis can be explained by the selection bias of our inclusion criteria which excluded many patients with discharge diagnosis of pneumonia, either due to nonavailability of culture report or negativity of culture of respiratory specimens. In end-stage kidney disease, Chen et al.[25] reported aerobic Gram-positive organisms' predominance (54%, with 67% of those S. aureus). However, in a study among the hemodialysis population by Slinin et al.,[26] no pathogen was specified in 81.8% of cases, Gram-negative bacteria isolated in 11.1%

cases (25% of those *P. aeruginosa*, the most common GNB), and 4.8% were attributed to Gram-positive bacteria. In our study, 87.5% (n = 7) cases were attributed to GNB, and GPB isolated in 12.5% (MSSA, n = 1) cases. *K. pneumoniae* was the most common organism (37.5%, n = 3), followed by A. baumanii (25%, n = 2). The organisms showed non-susceptibility to all the drugs tested.

TB remains an important cause of mortality and morbidity worldwide, especially in developing countries. Uremia is associated with impaired immunity due to various factors.^[27,28] Meta-analysis of hospital cohorts and regional registries showed that dialysis populations have an increased risk for active TB compared with the general population (pooled unadjusted rate ratio of 7.7).^[28] The same meta-analysis showed that after adjusting for demographic characteristics such as age and country of birth, the pooled rate ratio for TB risk decreased to 3.6 (95% confidence interval: 1.8–7.3). Country of birth was an important risk factor in dialysis populations rather than the dialysis state itself.^[28] In our study, the incidence rate of TB was 1023.9 per 100,000 per year, which is 5.3 times higher than the general population in India (193/100,000 in the year 2019) but lower than that in an older report from Indian HD populations (4200/100,000 per year).^[29,30] Incidence rates reported from other countries (5.7-115/100,000) are much lower than that in the Indian data.^[27,31-35] Similar to a previous report from India, pulmonary TB was more common than extra-pulmonary TB (66.6% and 33.4%, respectively) in our study.^[29] No drug-resistant TB was detected in the study.

Other less common infections noted in this study were SSTI, dengue fever, and isolation of MSSA from empyema in one patient. Isolates from SSTI include MSSA, multidrug-resistant *K. pneumoniae*, and *E. coli*. MSSA had good sensitivity to FQ, aminoglycosides, and clindamycin. Both *K. pneumoniae* and *E. coli* were resistant to penicillin, cephalosporins, aminoglycosides, and carbapenems.

The major limitation of the study is that it did not distinguish between community-acquired and hospital-acquired infections. There was no consideration of predisposing clinical conditions; thus, the reason for the very high incidence of UTIs could not be ascertained. Pneumonia incidence was exceptionally low because of selection of only microbiologically confirmed cases.

Conclusion

Our analysis provides a detailed spectrum of infections, pathogens, and their drug susceptibility in HD populations. The analysis included important non-access-related infections, which received less research attention from nephrologists. Though the bacterial spectrum remains the same over time, antibiotic resistance is ever-changing in UTIs. There is a trend of predominance of Gram-negative bacterial infections in CRBSI, but the commonly used empirical therapy with vancomycin plus aminoglycoside is still recommendable. Bacterial pneumonia and tuberculosis incidence were much higher than in the general population. There is a need for continuous surveillance for appropriate empirical antibiotic policymaking and to reduce the rising antibiotic resistance.

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Conflicts of interest

There are no conflicts of interest.

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