Original Article

Patterns of Drug Resistance in Infections among Hemodialysis Patients: A Cross Sectional Study from a Tertiary Care Hospital of Eastern India

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Abstract

Background : In patients undergoing hemodialysis, infection is the second most common complication following cardiovascular diseases. Antimicrobial resistance is spreading throughout the world and Multi Drug Resistant (MDR) organisms causing infection in this group of patients is also increasing. The main objective of the study was to to isolate the bacterial pathogens from various clinical samples collected from patients undergoing hemodialysis for more than 3 months and identify the drug resistant strains.

Materials and Methods : A cross-sectional study was conducted in the Department of Microbiology, Kalinga Institute of Medical Sciences (KIMS), Bhubaneswar for a period of 2 years (November, 2020 to October, 2022). End Stage Renal Disease (ESRD) patients, age >20 years undergoing HD who developed symptoms and signs of inflammation at different sites like jugular catheters and Arteriovenous Fistula (AVF) after 48 hours of insertion were included. Blood, sputum, urine, swab from infected catheter site and catheter tips were collected aseptically and subjected for automated culture and sensitivity testing for bacterial pathogens.

Results : Among 150 cases included in the study, 43.3% patients had bacterial infections. Staphylococcus aureus (26.4%) was the commonest bacterial isolate from blood sample and Klebsiella pneumoniae was commonest among all other clinical samples. In 24% MDR bacterial pathogens were isolated from clinical samples and Klebsiella pneumoniae was the most common MDR Gram-negative bacterial isolate. Methicillin Resistant Staphylococcus Aureus (MRSA) was isolated in 8% cases. In 11% pathogens were Extended Spectrum Beta Lactamases (ESBL) producers and 5% were Carbapenamase producers.

Conclusion : Effective infection control strategy and hand hygiene should be carried out to decrease infections in HD cases.

Key words : Hemodialysis, Infection Control, Infection, Multi Drug Resistant.

Chronic Kidney Disease (CKD) is defined as the existence of kidney damage or an estimated Glomerular Filtration Rate (eGFR) less than 60 ml/min/1.73 m^2 that lasts for 3 months or longer, regardless of the etiology. It is divided into six stages depending on glomerular filtration rate, with stage G5 End Stage Renal Disease (ESRD) being the final and most severe[1]. So, renal replacement therapy like hemodialysis, peritoneal dialysis etc is required for their treatment. Settings where several patients receive hemodialysis simultaneously, there is numerous potential for the spread of infectious organisms as the technique necessitates vascular access for extended periods of time.

Editor's Comment :

- Effective infection control practices have to be to decrese the infections in hemodialysis patients. Also for any infection proper antibiotics have to administered according to the antimicrobial susceptibility report.
- Escalation or de-escalation of antibiotics need to be followed to prevent MDROs.

It has been shown that healthcare workers' hands or contaminated tools, supplies, injectable drugs, ambient surfaces or gadgets can transmit infectious pathogens from patient to patient. Patients receiving maintenance hemodialysis are more likely to contract an infection because uremia is known to increase the susceptibility of ESRD patients to infectious pathogens by impairing cellular immunity, neutrophil function, and complement activation.

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Infections are the second most common cause of mortality and hospitalization after cardiovascular disease among these patients[2]. When compared to the general population, HD patients had a 6.3-8.2 times higher yearly infection mortality risk[3]. Chronic dialysis patients are at risk of infections caused by nosocomial Multidrug Resistant (MDR) pathogens exhibiting decreased susceptibility to many antimicrobials[4]. MDR is defined as non-susceptibility to at least one agent in three or more antimicrobial categories[5].

MDR organisms like Vancomycin Resistant Enterococci (VRE), Methicillin Resistant Staphylococcus Aureus (MRSA) and MDR Gram- negative rods are the predominant pathogens found in hemodialysis patients[6].

The majority of bacteremia incidents are linked to vascular access, particularly Central Venous Catheters (CVC). Coagulase negative Staphylococcus aureus and recently S aureus species resistant to Methicillin or Vancomycin (MRSA or VRSA) are the most common bacteria responsible for CVC associated bacteremia[7].

The primary aim of the study was to isolate and identify the bacterial pathogens in catheter tip, blood, swab from infected site, urine and sputum samples collected from patients undergoing hemodialysis for more than 3 months. The antibiotic susceptibility pattern of the isolated bacterial pathogens was observed for screening of the drug resistant strains.

Materials and Methods

A prospective cross sectional study was carried out in the Department of Microbiology in association with Department of Nephrology of Kalinga Institute of Medical Sciences, Bhubaneswar between November, 2020 to October, 2022 which included all End Stage Renal Disease (ESRD) patients undergoing dialysis during this period. Total 150 ESRD patients were included and different samples like catheter tip, sputum, urine, peripheral venous blood and swabs were collected for screening of the bacterial pathogens.

Inclusion Criteria :

ESRD Patients, age >20 years undergoing hemodialysis, who develop signs of inflammation at different sites like Jugular, Femoral, Subclavian catheters and AV fistula after 48 hours of insertion. Patients who develop fever, chills, headache, abdominal pain, diarrhea and hypotension and any other signs and symptoms suggestive of infection any time after 48 hours of insertion of central venous catheter during hospitalization and who have given their consent to participate in the study.

Exclusion Criteria :

Patients who have fever, chills, headache and signs of inflammation within 48 hours of insertion of catheter or prior to dialysis, patients in whom blood culture was positive before dialysis and patients who have not given their consent to participate in the study.

Sample Collection, Transport and Processing :

Catheter tip, swab from infected site of catheter, urine, sputum and peripheral venous blood were collected and processed as per the standard guidelines[8-11].

Peripheral venous blood were collected from two separate venepuncture sites (one from central line and one from peripheral line or both from peripheral lines) and incubated in BacT/ALERT (bioMerieux, USA). After the machine flagged bottle positive, the bottle was taken out and subcultured into Blood agar and MacConkey agar. Overnight incubation of plates was done at 37^{o}C in incubator[8-10].

Identification and antimicrobial susceptibility of isolates from all the samples were carried out with the Vitek 2 (bioMerieux, USA) system according to Clinical and Laboratory Standard Institute (CLSI) 2021 cut off points.Resistance detection was carried out using the advanced AES programme, which could identify and record resistance patterns utilizing MICs.

Detection of ESBL and MRSA :

It was confirmed by standard disc diffusion method according to CLSI M100 2022[12].

Detection of Carbapenamase producer was done by modified Carbapenem Inactivation Method (mCIM) in conjunction with EDTA- modified carbapenem inactivation method (eCIM) according to CLSI M100 2022[12].

Results

Klebsiella pneumoniae, *Staphylococcus aureus* (MSSA), *Staphylococcus aureus* (MRSA) *and Pseudomonas aeruginosa* were isolated from almost all the clinical samples. *Klebsiella pneumoniae* was the commonest aerobic bacterial isolate 32 (44.6%). *Staphylococcus epidermidis* 1 (0.6%) and *Staphylococcus hemolyticus* 9 (6%) were isolated only from peripheral venous blood.

From catheter tip, the bacterial pathogens isolated were *Klebsiella pneumoniae* (5%), *Acinetobacter baumannii* (3%), *Staphylococcus aureus (MSSA)*(3%), *Staphylococcus aureus (MRSA)*(3%) and *Pseudomonas aeruginosa* (1.6%). *Escherichia coli* 11

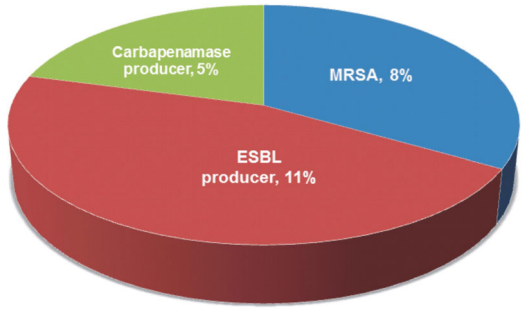

Fig 1 — *Drug resistant bacterial pathogens isolated from culture positive cases (n=104)*
MRSA: Methicillin Resistant Staphylococcus Aureus,
ESBL: Extended Spectrum Beta Lactamases

(12%) was the commonest isolate from urine sample.

Culture positivity of catheter tip was maximum by roll plate method 88 (58.7%) as compared to segment washing 28 (18.7%) which is also statistically significant.

Among the drug resistant bacterial pathogens isolated, Multidrug Resistant Organisms (MDRO) were commonest 25 (24%) followed by ESBL producers 12 (11%), MRSA 9(8%) and carbapenamase producers 4(5%)(Fig 1).

Isolation of ESBL producers were maximum from urine sample (10%) followed by sputum (2%) and peripheral venous blood (1.3%).

MRSA were mostly isolated from catheter tip (3.3%) followed by peripheral venous blood (2.6%), sputum (2%), swabs (1.6%) and urine (1%).

Carbapenamase producers were isolated from only peripheral venous blood sample (2.6%).

Klebsiella pneumoniae was the most common MDR Gram-negative bacterial isolate 10 (9%) from clinical samples followed by *Acinetobacter baumannii* 06 (5%), *Escherichia coli* 05 (4.8%), *Burkholderia cepacia* 03 (2.8%) and *Pseudomonas aeruginosa* 02 (1.9%)(Table 1).

Maximum susceptibility of MRSA isolates (100%) were seen for Daptomycin, Linezolid, Teicoplanin, Vancomycin and Nitrofurantoin. Resistance was maximum for Benzylpenicillin (100%). Susceptibility for Tigecycline, Gentamicin Cotrimoxazole and Erythromycin were 89%, 78%, 78% and 67% respectively. Least susceptibility was seen for Ciprofloxacin (44%), Clindamycin (44%) and Tetracycline (44%)(Fig 2).

Table 1 — *MDR Gram-negative bacterial pathogens from clinical samples showing culture positivity (n=104)*

MDRO (Multidrug resistant organisms)	Percentage
K pneumoniae	9%
A baumannii	5%
P aeruginosa	1.9%
A denitrificans	00
B cepacia	2.8%
E cloacae	00
E aerogenes	00
P mirabilis	0.9%
E coli	4.8%
E meningoseptica	00
Total	24%

Maximum susceptibility of ESBL producers was seen for Ceftriaxone (59%). Amikacin, Cefepime, Cefoperazone+sulbactam, Gentamicin and Ticaracillin+clavulanic acid were susceptible among 58% isolates (Table 2).

Resistance to Amoxyclav, ampicillin, cefoperazone+Sulbactam and ceftriaxone was commonly seen among the MDR pathogens like *Klebsiella pneumoniae, Proteus mirabilis* and *Pseudomonas aeruginosa* (Fig 3).

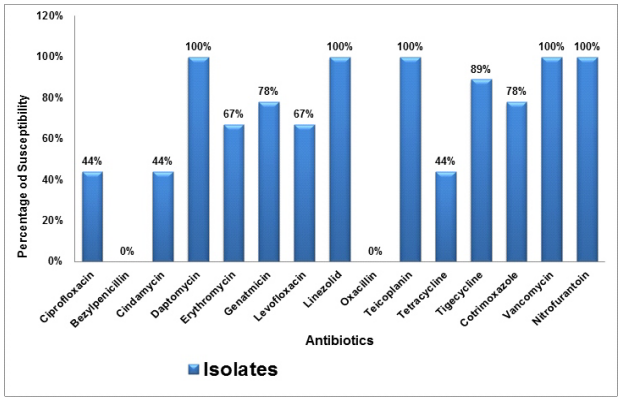

Fig 2 — Antibiotic Susceptibility pattern of MRSA (Methicillin resistant staphylococcus aureus) isolates

Table 2 — *Susceptibility pattern of ESBL producers*

Drugs/ MDR	AK	AMC	AMP	CPM	CPS	CTR	CIP	CL	ERT	GEN	IPM	MRP	NIT	PIT	TGC	COT	DRP	TCC	FO
ESBL (12)	58%	50%	41.7%	58%	58%	59%	50%	16%	41.7%	58%	41.7%	41.7%	55%	33%	33%	41.7%	41.7%	58%	55%

ESBL: Extended spectrum beta lactamases, AK: Amikacin, AMC: Amoxcillin + Clavulanic acid, AMP: Ampicillin, CPM: Cefepime, CPS: Cefoperazone + Sulbactam, CTR: Ceftriaxone, CIP: Ciprofloxacin, CL: Colistin, ERT: Ertapenem, GEN: Gentamicin, IPM:Imipenem, MRP: Meropenem, NA: Nalidixic acid, NIT: Nitrofurantoin, PIT: Piperacillin + Tazobactam, TGC: Tigecycline, COT: Cotrimoxazole, CAZ: Ceftazidime, DRP: Doripenem, TCC: Ticacillin + Clavulanic acid , FO: Fosfomycin

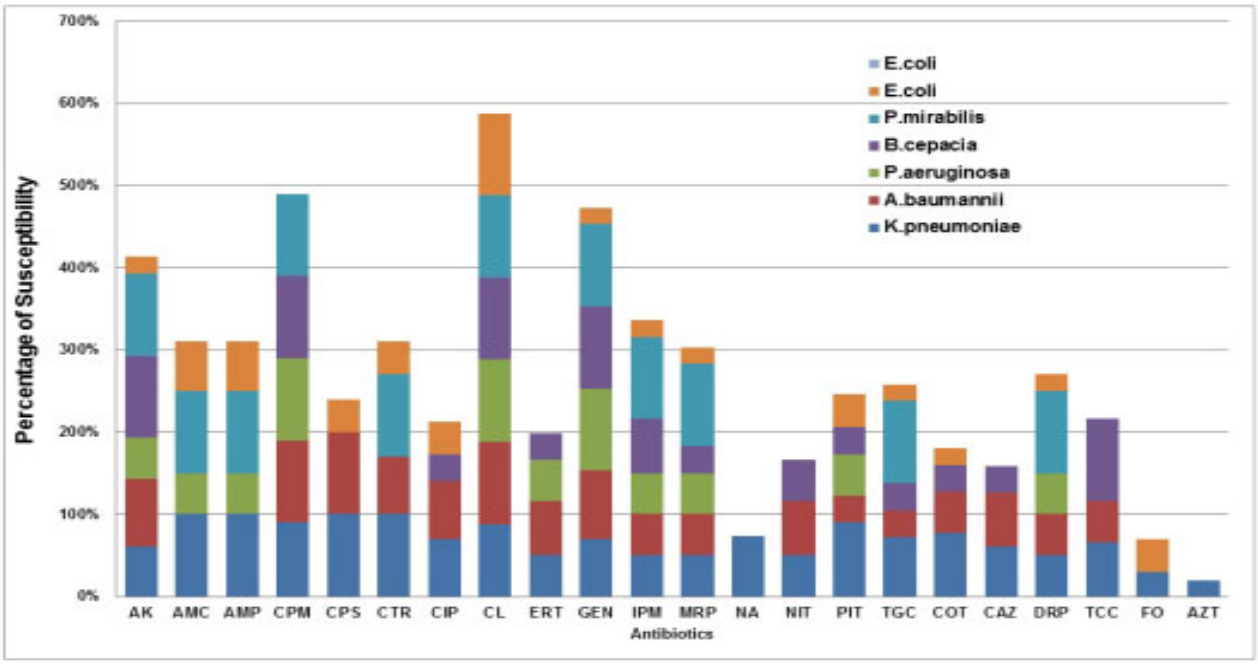

Fig 3 — Resistance pattern of MDR isolates

MDR: Multidrug resistant, AK: Amikacin, AMC: Amoxcillin + Clavulanic acid, AMP: Ampicillin, CPM: Cefepime, CPS: Cefoperazone + Sulbactam, CTR: Ceftriaxone, CIP: Ciprofloxacin, CL: Colistin, ERT: Ertapenem, GEN: Gentamicin, IPM:Imipenem, MRP: Meropenem, NA: Nalidixic acid, NIT: Nitrofurantoin, PIT: Piperacillin + Tazobactam, TGC: Tigecycline, COT: Cotrimoxazole, CAZ: Ceftazidime, DRP: Doripenem, TCC: Ticacillin + Clavulanic acid, FO: Fosfomycin

Discussion

Klebsiella pneumoniae was the commonest aerobic bacterial isolate (44.6%) in our study followed by MSSA (16.3%), *Escherichia coli* (14%) and MRSA (10.2%). Our findings can be compared with the study carried out by Alzhami SM, *et al* (2019) where the common bacterial pathogens isolated were *Klebsiella pneumoniae* (40%), *Staphylococcus aureus* (16.7%), MRSA (9.1%) and *Escherichia coli* (3%)[13]. However, the study carried out by Fysaraki M, *et al* 2013 revealed *Staphylococcus aureus* as the commonest bacterial pathogen (36%) followed by *Staphylococcus epidermidis* (17%), *Escherichia coli* (9%) and *Klebsiella spp* (4%)[4].

Among the bacterial pathogens isolated from culture positive cases, multidrug resistant Gram-negative bacterial pathogens (MDRO) were commonest (24%) followed by ESBL producers (11%), MRSA (8%) and Carbapenamase producers (5%). Calfee DP, *et al* 2013 and 2015, in their study found MDRO (16%) as the commonest drug resistant bacterial pathogen followed by MRSA (1.4%-27%)[3,14]. Alzhami SM, *et al* 2019 also found 9.1% MRSA from hemodialysis patients[13]. AbuTaha SA, *et al* 2022 got MDRO 75.4% and ESBL 1.69% in contrast to our observations[15]. Fysaraki M, *et al* 2013 found 18% ESBL producers among the *Escherichia coli* isolates[4].

Klebsiella pneumoniae was the commonest MDR gram negative isolate and also the most common carbapenamase producer which is in contrast to the observations of Patel G, *et al* (2008)[16].

Among the Gram-negative bacterial isolates, *Klebsiella pneumoniae* was the most common multidrug resistant pathogen (9%) followed by *Acinetobacter baumannii* (5%), *Escherichia coli* (4.8%), *Burkholderia cepacia* (2.8%) and *Pseudomonas aeruginosa* (1.9%). Sahli F, *et al* 2016 found in their study *Klebsiella pneumoniae* strains (22.7%) as most common multidrug resistant strains followed by *Acinetobacter baumannii* (9.1%).

All the MRSA isolates[9] of our study were 100% sensitive to Daptomycin, Linezolid, Teicoplanin, Vancomycin and Nitrofurantoin and 100% resistant to Benzylpenicillin. But all *Staphylococcus strains*[8] were Methicillin resistant in the study carried out by Sahli F, *et al* 2016[17]. In 67% *Staphylococcus aureus* isolates and 68% *Staphylococcus epidermidis* showed resistance to Methicillin in the study carried out by Fysaraki M, *et al* 2013[4].

In our study maximum resistance was seen in *Proteus mirabilis* followed by *Klebsiella pneumoniae* and *Burkholderia cepacia*. Resistance was commonly seen for Cefepime, Colistin, Gentamicin and Amikacin, Ciprofloxacin Piperacillin+Tazobactam. Vicas AP, *et al* (2008)[18] found maximum resistance to ampicillin/sulbactam, ceftazidime, piperacillin/tazobactam and ciprofloxacin among the MDRGN bacterial isolates.

Limitations of the Study :

The study involved a single hospital in one geographic area along with small sample size and thus represents single center experience. Isolation of bacterial pathogens from clinical samples could have been more but sometimes patients have received antibiotics prior to admission in the hospital as ours is a tertiary care hospital. We got the drug resistance pattern of the bacterial pathogens by phenotypic methods but could not confirm it by genotypic methods due to limited resources.

Conclusion

This study involved a single hospital in one geographic area along with small sample size and thus represents single center experience. Isolation of microbial pathogens from clinical samples could have been more but some samples were processed after the antibiotic therapy as ours is a tertiary care hospital and sometimes patients have received antibiotics prior to admission in the hospital.

The rise of MDR species, particularly MRSA and ESBL-producing bacteria, makes infection management even more difficult. MDRO are responsible for a large number of infections in our patients. It is vital that health care providers should prevent these infections by implementing and enforcing infection control policies in hemodialysis centers, as well as administering appropriate antibiotic medication with restricted usage and duration.

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Conflict of Interest : None

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