Original article

Prevalence of drug-resistant microbes in sepsis cases of catheter and fistula based haemodialysis

Rui Jianga, Waqas Ahmedb, Habiba Daudb, Dawood Ahmedc⇑, Salim Al-Rejaied, Muhammad Awaise,⇑, Irshad Muhammadf, M. Ijaz Khang,⇑, Mohammed M Jalalh, Osama M Alshehrii, Mater H. Mahnashij

aDepartment of Nephrology, Huzhou Central Hospital, Zhejiang, Huzhou 313003, PR China
bDepartment of Microbiology, The University of Haripur, Haripur, Pakistan
cDepartment of Medical Lab Technology, The University of Haripur, Haripur, Pakistan
dDepartment of Pharmacology and Toxicology, College of Pharmacy, King Saud University, Riyadh, Saudi Arabia
eDepartment of Biochemistry and Molecular Biology, Faculty of Sciences, University of Sialkot, Punjab, Pakistan
fSchool of Chemical Engineering, Sungyunkwan University, Suwon, South Korea
gDepartment of Mathematics and Statistics, Riphah International University I-14, Islamabad 44000, Pakistan
hDepartment of Medical Laboratory Technology, Faculty of Applied Medical Sciences, University of Tabuk, Tabuk, SA, Saudi Arabia
iDepartment of Clinical Laboratory Sciences, College of Applied Medical Science, Najran University, Najran, Saudi Arabia
jDepartment of Pharmaceutical Chemistry, School of Pharmacy, Najran University, Najran, Saudi Arabia

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Abstract

Background: Chronic stage renal disease is a severe disease of the kidney which affects people globally. According to the global burden of diseases in 2010, this disease has caused more deaths worldwide and due to the high death rate, the ESRD (end-stage renal disease) is now ranked up from 27th to 18th range in the list.

Methodology: Dialysis samples were collected from the Haripur city and surrounding areas. Samples were inoculated on different selective media for bacterial growth. In addition, different biochemical tests were also performed for identification, where as the resistance genes were identified through a polymerase chain reaction.

Result: Out of the total 100 dialysis patient’s blood samples, only 17 showed the presence of gram-positive bacteria i.e., Staphylococcus aureus while two shown the presence of gram-negative bacteria i.e., Klebsiella pneumoniae and Pseudomonas aeruginosa. While in molecular identification two antibiotic resistance genes muc and mecA belong to the Staphylococcus strain shown their presence.

Conclusion: A high infection rate has been observed in fistula-based hemodialysis (17(77.27%)) as compares to catheter-based hemodialysis (5(22.3%) with no significant difference of incidence between the groups (p > 0.05).

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1. Introduction

There are different causative agents of infection in hemodialysis patients. The most common of which were pathogens i.e., Staphylococcus aureus. The Staphylococcus infections were most common in hemodialysis patients because of its complication causing tissue, wound infections, meningococcal septicemia, and in severe cases, it is hard to treat infections. The rate of death and illness was also increased because of the Staphylococcus aureus. The Staphylococcus aureus infection in dialysis was found to be 1.45–66.0% of all the infections in dialysis (Mylotte and Tayara 2000). The bacteremia in dialysis patients was mainly due to the Staphylococcus aureus i.e., 27–39% (Danese et al., 2006). The infections in hemodialysis also occurred due to the gram-negative bacteria. The infection by gram-negative bacteria increases by 25% in hospital and hemodialysis blood infection (Albrecht et al., 2006). The rate of infection from different gram-negative bacterial strains was different, for example, Klebsiella 11.1%, Pseudomonas 5.1%, E. coli 49%,
obacter 13.1%, and Proteus mirabilis 6.1%. Due to transfusion of blood in dialysis, there were chances of developing viremia in patients including HCV and HBV viral infection. Bacteremia and viremia were the co-morbidities in dialysis patients. In the hemodialysis and peritoneal dialysis, there was another virus BKV that is also common and infect almost 90% of the patient population. In immunocompromised patients, the chances of reactivation of BKV virus are higher (Sharif et al., 2015). Therefore, the purpose of the current study was to find the prevalence of drug-resistant bacterial strains in hemodialysis patients.

End-stage renal disease (ESRD) is one of the major diseases that inflict a heavy economic burden on the globe (Weiner, 2009). In chronic kidney disease (CKD), the ratio of ESRD has been increased much during the last few decades and the only option of treatment has been limited to dialysis or a kidney transplant. The CKD has high prevalence rates among adults (Gorodetskaya et al., 2005; Kimmel and Patel, 2006) but it also affects children (Fadrowski et al., 2006). The CKD in the pre ESRD treatment phase demands a purpose of the current study was to find the prevalence of drug-resistant bacterial strains in hemodialysis patients.

The incidence and prevalence of CKD and ESRD are increasing at a much during the last few decades and the only option of treatment has been limited to dialysis or a kidney transplant. The CKD has high prevalence rates among adults (Gorodetskaya et al., 2005; Kimmel and Patel, 2006) but it also affects children (Fadrowski et al., 2006). The CKD in the pre ESRD treatment phase demands

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2. Methodology

This study was duly approved by ethical and biosafety committee of The University of Haripur before the onset of the study. This study confirms the declaration of Helsinki and informed consent were taken from the participants or their legal representatives after the sharing the significance of the study. The hemodialysis patients were selected from District Headquarter Hospital, Haripur, and Kidney Centers of Abbottabad and Rawalpindi Districts. The blood samples were taken from all the dialysis patients of the said areas. There is no restriction of age and gender rather this research study comprised all age groups regardless of gender specificity. This study focused mainly on checking the prevalence rate between male and female patients, insertion devices that were used during dialysis, and the infection rate among them. This study was carried out from June 2018 to February 2019 and during this time interval blood samples were also taken from the patients. A total of 100 patients were selected and blood on dialysis samples was taken from hemodialysis patients by the help of sterile syringes and blood was collected in sterile tubes. After this, these collected samples were transferred to the Microbiology laboratory of the Department of Microbiology, University of Haripur. Selective media were used for culturing the different bacteria strains. The selective media used for Staphylococcus aureus, Klebsiella pneumoniae and Klebsiella pneumoniae were mannitol agar, eosin methylene blue agar and cetrimide agar, respectively.

3. Biochemical analysis

Biochemical tests were also performed for further confirmations. To check antibiotic resistance Kirby Baur method was used. Antibiotics used to detect antibiotic resistance were amoxicillin-clavulanic acid, cefotaxime oxacillin, ceftriaxone, erythromycin, vancomycin, ceftazidime, tetracycline and aztreonam.

4. Molecular analysis (PCR)

DNA extraction was done by boiling method for chromosomal extraction while in case of plasmid extraction WizPrep plasmid kit method were used. In kit method 1.5 ml of bacterial cell culture in a centrifuge tube and centrifuge 13000 rpm for 1 min. Add 200 µl PD1 buffer and vortex it. Then add 200 µl PD2 and 300 µl PD3 buffer stepwise and inverted tube many times. After PD3 buffer centrifuge the tube for 10 min. Take supernatant from microcentrifuge tube to the spin column and centrifuge it. Repeating the spin column and centrifuge step several times. Wash the spin column with 600 µl wash buffer and centrifuge it. Dry the spin column and add 50 µl of elution buffer. After keeping at room temperature for 3 min. Centrifuge the spin column at 13000 rpm for 1 min and elute the DNA. PCR amplification of the resistance genes was done by a reported method in the case of Staphylococcus aureus. The mecA and nuc amplifications were done according to Poulsen et al. (2003) and Zhang et al. (2005). The PCR amplified fragment length for the mecA and nuc was 147 bp and 253 bp, respectively. While in the case of ESBL gene in Klebsiella pneumoniae the primer was user defined. The PCR amplified fragment length for the ESBL related genes TEM1 and blaoSHV were 208 and 206 bp, respectively. The primers used for the detection of different antibiotic resistance genes in isolated S aureus are given in Table 1. The primers used for the detection of TEM1 and blaoSHV genes in Klebsiella pneumoniae were designed using the online primer designing tool Primer3 (Table 1).

For the PCR reaction mixture in the case of Staphylococcus aureus, a total volume of 25 µl included 16 µl nuclease-free water, 1 µl each of the forward and reverse primer Spp master mix and 2 µl of the DNA template. While in case of the Klebsiella pneumoniae reaction mixture of 25 µl included 20 µl nuclease-free water, 1 µl each of the forward and reverse primer, 4 µl master mix and 5 µl DNA template. In PCR thermal profile of Staphylococcus aureus and Klebsiella pneumoniae were give below in Table 2.

5. Result

The Staphylococcus aureus on mannitol agar showed yellow colonies and media fermentation further identified the bacteria. Klebsiella pneumoniae on cetrimide agar showed pink colonies on eosin blue agar and Pseudomonas aeruginosa showed white colonies on cetrimide agar, but Staphylococcus epidermidis showed white colonies and did not show media fermentation.

Out of 100 hemodialysis patients, 17% patients showed positive Staphylococcus aureus, 2% showed gram-negative bacteria and only 1% case of Staphylococcus epidermidis and 2% Pseudomonas aeruginosa and Klebsiella pneumoniae were found during this study. There were 78% of samples that did not show any kind of bacterial growth. The sepsis rate in hemodialysis was found to be 22% out of 100% (Fig. 1).

In these sepsis cases, the catheter and fistula ratio are 5 and 12 in Gram positive bacteria while in the case of Gram-negative Pseudomonas and Klebsiella were 0 and 2 in catheter and fistula while one individual was found to be infected with Staphylococcus epidermidis in fistula based hemodialysis (Table 3).

Out of 100 enrolled patients, there were about 22(22%) patients having dialysis through the catheter and 78% dialysis through fistula based haemodialysis. Sepsis confirms cases with sepsis (Table 4). There was no significant difference observed in the distribution of sepsis cases between both gender (p > 0.05) shown in Table 4.
In correlations analysis, different risk factors that were associated with each other were also studied. The correlation factors examined were the types of catheter or fistula, family history, infections during dialysis, and hypertension. Some factors did not show significance value, while some were observed below the average. The family history of kidney disease with HCV co-infection showed significance \((p < 0.01)\), infection during dialysis with other infection (sore throat, fever, flu) were also significant \((p < 0.01)\). Similarly, hypertension and diabetes were also associated significantly \((p < 0.05)\).

The methicillin resistance \(\textit{Staphylococcus aureus}\) showed complete resistance to amoxicillin-clavulanic acid, cefotaxime ceftriaxone, erythromycin, aztreonam, and ceftazidime. MRSA showed susceptibility to vancomycin \((4)\) oxacillin \((1)\) and tetracycline \((1)\). The antibiotic resistance patterns are shown in Fig. 2 below graph 2.

The \(\textit{Pseudomonas aeruginosa}\) did not show any susceptibility against antibiotics. The antibiotics showing total resistance were amoxiclav clavulanic acid, cefotaxime, oxacillin, ceftriaxone, vancomycin, aztreonam, tetracycline and ceftazidime. The only erythromycin showed intermediate resistance \((\text{Fig. 3})\).

The \(\textit{Klebsiella pneumoniae}\) showed resistance to most of the antibiotics that were used and include amoxiclav clavulanic acid, cefotaxime, oxacillin, ceftriaxone, vancomycin, aztreonam, tetracycline and ceftazidime. But tetracycline showed total susceptibility. And erythromycin showed intermediate susceptibility. The different antibiotic resistance patterns are shown in Fig. 4.

The \(\textit{Staphylococcus epidermidis}\) did not show complete resistance against antibiotics. In the case of amoxiclav clavulanic acid, oxacillin, ceftriaxone, vancomycin, aztreonam, and cefazidime. But in the case of \(\textit{Staphylococcus epidermidis}\), it did not show susceptibility against any drugs \((\text{see Fig. 5})\).

In the total 17 samples of \(\textit{S. aureus}\), \(\text{nuc}\) was positively detected in 1 sample only, while in the other samples \(\text{nuc}\) was not detected.

### Table 1
**PCR primers sequences for the detection of selected resistance genes.**

| Primer | Gene   | Sequence                                      | Product size (bp) | Reference         |
|--------|--------|-----------------------------------------------|-------------------|-------------------|
| **\(\textit{Staphylococcus aureus}\)** | FP     | \(\text{nuc}\) | 5'-TCAGCAAATGCATCACAACAG-3' | 255 | Poulsen et al.,2003 |
|        | RP     | \(\text{mec}\) | 5'-CGTAAATGCACTTGGCCTTGGAG-3' | 147 | Zhang et al.,2005 |
| **\(\textit{Klebsiella pneumoniae}\)** | FP     | TEM 1 | 5'-GGCGCCTTCTCATAGCTCAC-3' | 208 |                |
|        | RP     | \(\text{blaSHV}\) | 5'-GGCTCCCATGATAGCACCTG-3' | 206 |                |

### Table 2
**Thermal profile for a polymerase chain reaction.**

| Step               | Initial Denaturation | Denaturation | Annealing | Extension | Final Extension |
|--------------------|----------------------|--------------|-----------|-----------|-----------------|
| Initial Denaturation | 95 °C 5 min          |              |           |           |                 |
| Denaturation        | 95 °C 30 sec         |              |           |           |                 |
| Annealing           | \(\text{nuc/mecA}\)   | 55 °C 30 sec | 57 °C     | 72 °C     |                 |
|                    | TEM1/blaSHV          |              |           |           |                 |
| Extension           | 72 °C 30 sec         |              |           |           |                 |
| Final Extension     | 72 °C 10 min         |              |           |           |                 |

**Fig. 1.** Graphical representation of bacterial isolates.

In correlations analysis, different risk factors that were associated with each other were also studied. The correlation factors examined were the types of catheter or fistula, family history, infections during dialysis, and hypertension. Some factors did not show significance value, while some were observed below the average. The family history of kidney disease with HCV co-infection showed significance \((p < 0.01)\), infection during dialysis with other infection (sore throat, fever, flu) were also significant \((p < 0.01)\). Similarly, hypertension and diabetes were also associated significantly \((p < 0.05)\).

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The \(\textit{Staphylococcus epidermidis}\) did not show complete resistance against antibiotics. In the case of amoxiclav clavulanic acid, oxacillin, ceftriaxone, vancomycin, aztreonam, and cefazidime. But in the case of \(\textit{Staphylococcus epidermidis}\), it did not show susceptibility against any drugs \((\text{see Fig. 5})\).

In the total 17 samples of \(\textit{S. aureus}\), \(\text{nuc}\) was positively detected in 1 sample only, while in the other samples \(\text{nuc}\) was not detected.

### Table 3
**Catheter and Fistula Based Distribution of Bacterial Species.**

| Species                | All | Fistula | Catheter | \(\chi^2\) | \(P\) |
|------------------------|-----|---------|----------|------------|------|
| \(\textit{Staphylococcus aureus}\) | 17  | 12(63.1%) | 5(22.7%) | 0.8        | >0.05|
| \(\textit{Staphylococcus epidermidis}\) | 1   | 1(100%)  | 0(0%)    | 0.0        |      |
| \(\textit{Pseudomonas aeruginosa}\) | 2   | 2(100%)  | 0(0%)    | 0.0        |      |
| \(\textit{Klebsiella pneumoniae}\) | 2   | 2(100%)  | 0(0%)    | 0.0        |      |

### Table 4
**Prevalence of Sepsis in Catheter and Fistula Based Haemodialysis and gender.**

| Sepsis Status | P-value | OR(95%CI) |
|---------------|---------|-----------|
| Positive      | N = 22  |            |
| Negative      | N = 78  |            |

| Mode of route | P-value | OR(95%CI) |
|---------------|---------|-----------|
| Catheter      | 5(22.7%) | 77(173)  |
| Fistula       | 22(28.2%)| 71(173)  |
| Gender        |         |          |
| Male          | 17(77.3%)| 12(28.7%)|
| Female        | 56(76.8%)| 22(28.7%)|

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Fig. 2. Antibiogram of *Staphylococcus aureus* isolates against selected antibiotics.

Fig. 3. Antibiogram in *Pseudomonas aeruginosa* isolates against selected antibiotics.

Fig. 4. Antibiogram in *Klebsiella pneumoniae* isolates against selected antibiotics.
Same is the case of the mecA, out of 17 samples only 1 sample the mecA was positively detected. The nuc gene detection was not possible in all samples because of the non-optimal experimental condition or the absence of nuc gene in some Staphylococcus aureus samples.

The amplification of ESBL related genes from Klebsiella pneumoniae has not been observed therefore these strains do not have ESBL gene (see Figs. 6 and 7).

Fig. 5. Resistance pattern of Staphylococcus epidermidis isolates against selected antibiotics.

Fig. 6. PCR of nuc gene.

Fig. 7. PCR of mec A gene.
6. Discussion

The CKD, which is currently renowned as a major public health problem, can be detected by simple biochemical tests including creatinine base estimate of glomerular filtration rate. Estimates in Asia and Australia indicate that the problem is of the same magnitude in these countries (Chen et al., 2005; Chadban et al., 2003). CKD is considered a dangerous clinical condition for two main reasons: firstly because of the renal impairment which may preclude to the development of ESRD, the disease stage where dialysis and transplantation are needed. Secondly, because it further triggers the risk of developing cardiovascular complications. Independent from these risk factors patients with 4–5 CKD have a death risk for cardiovascular complications which is 2–4 times higher than that of coeval general populations, whilst patients with ESRD have a 100 times higher risk (Baigent et al., 2000).

Sepsis ranks as the tenth leading cause of death in the United States. Sepsis and bacterial infections are very common in ESRD patients, which are followed by cardiovascular diseases, therefore, these infections are the leading cause of death in patients with ESRD (Collins et al., 2014). The diagnosis of sepsis in such patients is often challenging and requires a high index of suspicions. Most studies on sepsis ranging from the sensitivity of systematic response syndrome criteria (Jaimes et al., 2003) to lactate clearance (Nguyen et al., 2004) and optimal fluid therapy have looked in the general population.

Methicillin resistant Staphylococcus aureus has become a major public health problem all over the world. It is correlated with incremented morbidity and mortality compared to other pathogenic bacteria. The elevated colonization rates lead to the incrimination of infection rates in the community and medical centers which leads to a significant increase in the treatment costs (Liu et al., 2008). The majority of the researcher in this field suggested that the mecA is present in all the MRSA strains and is known to encode penicillin-binding protein 2a (PBP2a) which has a low tropism to all the β lactam antibiotics is the corner stone responsible for producing MRSA phenomenon. Molecular amplification of the mecA is recognized as a benchmark to diagnose MRSA in the community as this gene is highly conserved among Staphylococcus species (Abbas, 2012).

Recently, a coworker from a tertiary care hospital known to carry MRSA with the nuc, mecA duplex PCR method. The result was nuc negative MRSA conclusion. Conventional screening of this clinical sample revealed a MRSA positive outcome. This discrepancy could be explained by primer annealing site polymorphism or partial deletion of the nuc gene. These findings are in agreement with our studies, in which only one sample was positive out of 17 samples despite showing antibiotic resistance on the disc diffusion test.

Similarly, Klebsiella pneumoniae and Escherichia coli remain the major ESBL producing organism isolated worldwide, which are recommended to be routinely tested for and reported by the clinical and laboratory standard institute (CLSI 2006). Klebsiella pneumoniae is one of the most common organisms associated with hospital-acquired infection. On molecular analysis, we could not amplify ESBL related blaSHV and TEM1 genes in Klebsiella pneumoniae during this study, which indicates that some other related genes may be involved in causing antibiotic resistance in the Klebsiella pneumoniae strains.

7. Conclusions

In hemodialysis, the chances for survival were low because of a high risk of infections. Physicians control the infection by prescribing antibiotics but their massive use causes the development of antibiotics resistant bacteria. MRSA, the most dangerous bacterial specie and ESBL based gram-negative bacteria cause sepsis in hemodialysis patients. The process of hemodialysis is performed in two ways either by catheter or by fistula, whereas the use of catheter is life-threatening due to venous access. The mecA is present in MRSA and there is no ESBL gene found in Klebsiella pneumoniae. Maintenance of hygienic conditions in hemodialysis center and also the precautionary measures must be undertaken by the staff to reduce the chances of infection. The presence of MRSA in haemodialysis patients is an alarming situation to be considered for kidney patients. The CKD is severe and irreversible kidney damage in which kidney is allowed to function by an artificial machine to support life.

8. Recommendations

The infection cases in dialysis centers are on the rise nowadays therefore we suggest the following recommendation.

- Hygienic conditions should be strictly maintained to control the incidence of infections.
- To overcome the infections, the staff must undergo certain mitigating measures like cleaning of the dialysis machine that must be ensured.
- Proper maintenance of the drainage system by the dialysis centers to avoid bacterial spread/contamination.
- To control the antibiotics resistance caused by superbugs, alternative techniques including phage therapy, nanotechnology and small anti-virulence particles can be used to disarm the pathogenic bacteria.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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