ORIGINAL ARTICLE

Trends in Antimicrobial Resistance Pattern of *Klebsiella* Bacteremia over a 6 Years Period (2010-2015) in a Hemodialysis Centre in Pakistan

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Abstract

Background
Klebsiella spp. is the commonest cause of bacteremia in dialysis patients from our center. A rising trend of antimicrobial resistance among *Klebsiella* has been reported from Pakistan. We studied the trends of antimicrobial resistance over 6 years in dialysis patients.

Methods
Sindh Institute of Urology and Transplantation (SIUT) is a 750 bedded tertiary care hospital in Karachi, Pakistan. Around 500 patients are offered outpatient dialysis daily.

We did a retrospective data analysis of all blood cultures sent from outpatient hemodialysis unit with isolation of *Klebsiella* spp. in the years 2010, 2012, 2014 and 2015. The resistance pattern of ceftriaxone, piperacillin-tazobactam, ciprofloxacin, trimethoprim-sulfamethoxazole, amikacin and imipenem were compared over a 6 years' period.

Results
A total of 27,852 blood cultures were received during the study years, out of which 19670 (70.6%) were positive for any microbial growth. Around 5325 (27%) were *Klebsiella* spp. There was an increase in percentage of *Klebsiella* spp bacteremia over the years, range from 19-35%. The antimicrobial sensitivity pattern changed over years. Resistance was lowest against imipenem in 2010 around 1%, which increased to 19% in 2015.

Conclusion
There is a gradual rise in *Klebsiella bacteremia* in dialysis unit. Resistance to broad-spectrum antimicrobials has increased significantly with around twenty-fold increase in imipenem resistance over the last 6 years. We need a robust stewardship program for judicious use of antimicrobials and better infection control measures to contain increasing resistance.

Introduction

Bloodstream infections (BSIs) are among the major causes of morbidity and mortality worldwide.[1] BSIs are the tenth leading cause of death according to a large surveillance study in United States.[2] Patients on hemodialysis are on an increased risk of blood stream infections, particularly those on temporary venous access.[3] According to The Joint Commission Report, between 2001-2011 catheter-related BSI rates are high, ranging from 7.4 to 12.2 per 1000 central line days in low and middle income countries as compared to 1.3-2.1 per 1000 central line days in high income countries.[4]

Klebsiella pneumoniae is a major nosocomial organism causing blood stream infections and found to be associated with significant mortality.[5] In patients on hemodialysis, studies reported *Klebsiella species (spp.)* to be one of most common causative organism among gram negative bacteremia.[6,7,8] Kalam *et al* from our center, studied gram negative BSIs with 77% of patients on hemodialysis, they found *Klebsiella* spp. as the most frequent organism isolated.[9]

Along with increasing frequency of *Klebsiella* infections, there is a concern of resistance to antimicrobials which may complicate their management. In US, the prevalence of multidrug-resistant *Klebsiella* spp. is between from 0.5%–17%.[10] A rising trend of resistance to most antimicrobials in clinical isolates of *Klebsiella* spp. has also been reported from Pakistan.[11] Khan *et al* reported *Klebsiella pneumoniae* as the most common organism showing resistance to carbapenems.[12]

Little is known from our part of the world regarding the frequency and resistance pattern of *Klebsiella* spp. bacteremia in patients on hemodialysis. With the emergence of multi-resistant organisms, antimicrobial treatment has become difficult whereas accurate knowledge of antimicrobial sensitivity is necessary for timely administration of appropriate empirical therapy. This study was conducted to know the trends of frequency and antimicrobial resistance in *Klebsiella* spp. in patients on hemodialysis. It will not only help the treating physician to choose appropriate empirical antibiotics but also judicious use of antimicrobials and better infection control measures can effectively be implemented.

Methods

This is a retrospective observational study, conducted at Sindh Institute of Urology and Transplantation (SIUT) Karachi, Pakistan. SIUT is a 750 bedded tertiary care hospital mainly

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caters to renal diseases and transplantation. It is the largest hemodialysis center of Pakistan where an average of around 500 hemodialysis done per day as outpatient.

The data was retrieved from the microbiology department. All blood cultures sent from hemodialysis unit which were positive for *Klebsiella* species were taken. Cultures were retrieved from the following years 2010, 2012, 2014 and 2015 for analysis.

Antibiotic sensitivity of *Klebsiella*. spp. isolates were determined on Muller Hunton agar plates by Kirby–Bauer disc diffusion method. Isolates were declared as sensitive or resistant on the basis of the zone of inhibition as determined by the criteria of Clinical Laboratory Standards Institute against the following antibiotics: ceftriaxone, ciprofloxacin, piperacillin-tazobactam, amikacin, trimethoprim-sulfamethoxazole and imipenem.

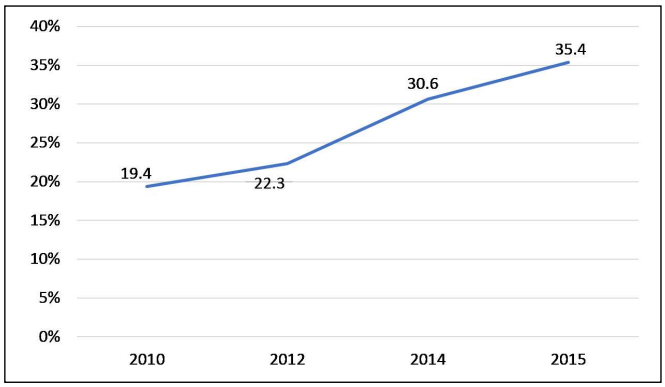

Fig 1. Frequency of *Klebsiella spp. bacteremia* in percentages over 6 years period.

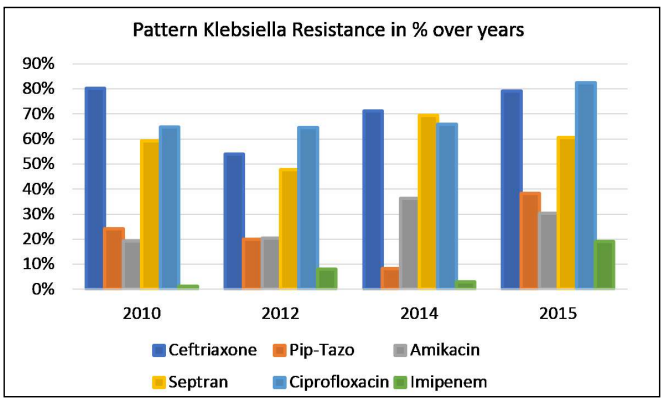

Fig 2. The resistance pattern of *Klebsiella* spp. bacteremia in percentages over 6 years

Results

A total of 27,852 blood cultures were received during the study years, out of which 19670 (70.6%) were positive for any microbial growth. A total of 5325 (27%) blood cultures grew *Klebsiella* spp. The frequency of *Klebsiella* spp. bacteremia over different years ranges from 19.4 to 27% as shown in Table 1 and Figure 1. The antimicrobial sensitivity over different years is represented in Figure 2. Resistance was lowest against imipenem in the year 2010 (1.19%) which gradually increased as 8% and 19% in the years 2012 and 2015 respectively. For piperacillin-tazobactam the resistance was around 20-30% between 2010-2014, it surged to reach 40% in 2015. High resistance was noted to ceftriaxone and ciprofloxacin in range of 70-80% through out.

Discussion

Klebsiella bacteremia accounted for 4-15% of all blood stream infections.[11] In our patient cohorts we observed a rising frequency of *Klebsiella* BSI from 19 % to 35% over the span of 6 years. Gram negative central line BSI has been increasing in frequency worldwide. Marcos *et al* reported a rising trend of gram negative BSI over an 18 years' time among patients with central lines. They argued that increasing use of antibiotics and prolonged hospital stay with resultant colonization may lead to more infections with gram negative bacteria.[7] Our center caters to renal and urological diseases. It is highly plausible that majority of infections in our patient population originate from urinary tract, hence it can be concluded that our hospital environment is colonized with *Enterobacteriaceae* and other gram negative organisms. The patients on hemodialysis have frequent contact with hospital environment and also get exposed to antibiotics often due to different infections. These may be the reasons behind increasing frequency of gram negative blood stream

Table 1. Year wise breakdown of blood cultures sent and positive along with Klebsiella spp.

Year	Total Number of Isolates Sent	Number of Isolates Positive	No of *Klebsiella* spp isolates	Percentage of *Klebsiella* spp
2010	6933	5179	1004	19.4%
2012	6001	4218	940	22.3%
2014	7478	5458	1675	30.6%
2015	7440	4815	1706	35.4%
Total	27852	19670	5325	27%

infections in our patient cohort.

We observed a rising trend of resistance among *Klebsiella* isolates which has become a matter of concern worldwide. According to World Health Organization, *Enterobacteriaceae* particularly *Klebsiella* spp are the organisms which need urgent new antibiotics due to widespread resistance.[12] A study from Karachi reported 50% of clinical isolates of *Klebsiella pneumoniae* were extended spectrum beta lactamase (ESBL) producing strains.[11] A meta-analysis from 55 studies over the past nine years showed a very high prevalence of ESBL producing *Enterobacteriaceae* (around 40%) from Pakistan.[13] Another study by Khan *et al* showed *Klebsiella* spp to be the most common organism showing resistance to carbapenems, majority of the isolates produce New Delhi metallo-beta-lactamase 1 (NDM-1) enzyme which make them extensively drug resistant.[14]

In our patient cohort we found a very high resistance (around 60-80%) to cephalosporins and ciprofloxacin in *Klebsiella* isolates as compared to reports from other tertiary care hospital of Karachi where it was reported was 30-50%.[15] We also found that this has remained prevalent over the last 6 years with negligible change in the pattern. Our patient cohort with renal diseases may get multiple exposures to both fluoroquinolones and cephalosporins which are commonly used in urinary tract infections, this may explain a continuous prevalence of very high resistance of these antibiotics in this population. Secondly, frequent contact with hospital environment is one of the risks for acquiring repeated infections. Agarwal *et al* showed that with repeated infections among *Klebsiella pneumoniae* there is a 1.14 times increase risk of these organisms to become resistant to antibiotics.[16]

It has been observed that Pakistan is considered top among countries where carbapenem consumption is high i.e. 1.8 per 1000 population in comparison to United States where the consumption is around 0.3 per 1000 population.[17] Studies showed that increase antibiotics consumption accelerate development of resistance.[18] We observed that there is an alarming rise in piperacillin/tazobactam (from 20% to 40%) and imipenem resistance (from 1% to 19%) in our study over 6 years' time. Kalam *et al* also reported increase in carbapenem resistance in patients with gram negative bacteremia from our center, with 42% to carbapenems.[9]

The patients on hemodialysis are at increased risk of infections owing to frequent hospital visits, direct access to major vessels and underlying organ failure, which may render them partially immunocompromised. In addition to multiple antibiotics exposure, biofilm formation around dialysis lines may be one of the factors leading to acquiring resistant organisms in this patient population. Lastly but very importantly breach in infection control practices during handling of dialysis lines or fistula needles may lead to infections with environmental pathogens of the hospital.

The limitation of our study is that it is a retrospective chart review where clinical data is not included. Furthermore, blood cultures sent were only analyzed and we could not extrapolate them with clinical episodes, that is why there is a high frequency of positive cultures seen. More studies to look into the clinical features, risk factors and mortality of *Klebsiella bacteremia* in hemodialysis population can help us better understand the disease pattern and its appropriate management. However, it is the first study from Pakistan focusing on the resistance pattern of *Klebsiella* spp. bacteremia in patients on hemodialysis.

In conclusion there is gradual rise in the frequency of *Klebsiella spp.* bacteremia over 6 years period in hemodialysis patients with an alarming rise in carbapenem resistance. Looking at the trends of resistance pattern we can conclude that carbapenems should be the empirical antibiotic of choice, however prompt culture retrieval and de-escalation to narrow spectrum antibiotics can prevent rising resistance.

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