Original Article

A retrospective study of the changing trends of antimicrobial resistance of *Klebsiella pneumoniae* isolated from urine samples over last 3 years (2012-2014)

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Abstract

Background: In our country, the problem of antibiotic resistance is compounding because of overuse and misuse of antibiotics. There is no systematic national surveillance of antibiotic resistance and insufficient data are available to quantify the problem. **Objectives:** To study the changing pattern of antimicrobial resistance of *Klebsiella pneumoniae* isolates from patients of urinary tract infections over last 3 years. **Materials and Methods:** A retrospective, record-based study carried out based on the records culture sensitivity reports of indoor patients, during past 3 years (2012-2014). The type of organisms most common in urine sample was noted, and the drugs still effective for the particular organism were noted. **Results:** *Klebsiella* was the second most frequent isolate throughout the 3 years (14%) of the total isolates). Analysis of the results year wise indicated that the lowest percentage of resistance was manifested against imipenem between 11.94% (2012) and 13.75% (2014). Over the successive years, resistance to ceftriaxone tends to increase from 74.95 % (2012) to 81% (2014). *Klebsiella* showed very high resistance 90.78% (2012) and 95.63% (2012) to co-trimoxazole and tetracycline, respectively with increasing trend to absolute resistance to both groups over the 3 years period. On an average over the 3 years *Klebsiella* showed a high amount of resistances to fluoroquinolones (72.71%) and aminoglycosides (76.22%). While multi-drug resistant *Klebsiella* range between 65% (2012) and 67% (2014). **Conclusion:** The antimicrobial resistance patterns are constantly evolving and vary from region to region it has become a necessity to do constant antimicrobial sensitivity surveillance. This will help clinicians to provide safe and effective empirical therapies.

Key words: Antimicrobial resistance, *Klebsiella pneumoniae*, urinary tract infections

INTRODUCTION

Urinary tract infections (UTIs) are one of the commonly encountered diseases in developing countries with an estimated annual global incidence of at least 250 million.[1] In most instances, the growth of more than 105 organisms/ml from a properly collected smidstream "clean-catch" urine sample indicates infection.[2] Excessive and/or inappropriate use of antibiotics in treating UTIs is responsible for the emergence and spread of multi-drug resistant (MDR) urinary bacteria. Epidemic and endemic nosocomial infections caused by *Klebsiella pneumoniae* are leading causes of morbidity and

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mortality.[3] There are three mechanisms that can cause antibiotic resistance: Prevention of the interaction of the drug with target organisms, decreased uptake due to either an increased efflux or a decreased influx of the antimicrobial agent, and enzymatic modification or destruction of the compound.[4] *Klebsiella. spp*. are often resistant to many antibiotics, including cephalosporins and aminoglycosides.[4] In UTI cases, antibiotic treatment is often started empirically, empirical first-line treatment of uncomplicated UTI should preferably be with an antibiotic to which resistance is low and which has a low capacity for co-selection of resistance and a low impact on the normal intestinal flora.[5,6] Resistance pattern of microorganisms vary from country to country, state to state, large hospital to small hospital and hospital to community. The estimation of local etiology and susceptibility profile could support the most effective empirical treatment.[7] In our country, the problem of antibiotic resistance is compounding because of overuse and misuse of antibiotics. There is no systematic national surveillance of antibiotic resistance, and insufficient data are available to quantify the problem. The aim of this study was to evaluate the *in vitro* resistance pattern to commonly used antimicrobial agents. This study will further help in formulating the most optimal empirical treatment regimen for UTI cases while awaiting culture sensitivity (C/S) reports with minimal therapeutic failure. It also reflects changes in the susceptibility pattern of the uropathogen *Klebsiella. spp*. over the years in this area, implying the need for periodic monitoring to decrease the number of therapeutic failures and to add on the effort to contain the increasing antibiotic resistance.

MATERIALS AND METHODS

A retrospective, record-based study was carried out in the department of pharmacology in collaboration with Microbiology department of a teaching tertiary care hospital. The study was carried out based on the records of (C/S) reports of indoor patients with UTI, acquired during their stay in hospital, during past 3 years from January to December from years 2012 to 2014 admitted in wards of Rajindra Hospital and Government Medical College Patiala, a tertiary care 1100 bedded hospital. Permission was taken from Ethical Committee and in charge of microbiology laboratory prior to the study. All the C/S reports of urine samples, maintained in the record registers of Microbiology laboratory received from various wards during the period 2012-2014 were included and analyzed. Reports of Isolates from repeat culture of previously recruited patients and isolates identified as commensals or contaminants were excluded from the study. No of reports/year for 3 years of urine samples which were already registered were noted. Only reports with positive *Klebsiella. spp*. C/S report were considered for this study. Positive reports for *Klebsiella. spp*. out of total number of urine samples positive for the years 2012, 2013, and 2014 were 161 (947), 200 (1058), and 206 (1102), respectively. The sample size for the present study was 567 for the 3 years. The data were collected year wise starting from the year 2012. The provisional diagnosis was noted.

Antibiotic sensitivity pattern of *Klebsiella. spp*. isolates was determined on Muller Hinton agar plates by Kirby–Bauer disc diffusion method. Isolates were declared as sensitive or resistant on the basis of the zone of inhibition following the criteria of clinical laboratory standards Institute.[8] The antibiotics tested were broad-spectrum penicillin, a third-generation cephalosporin, quinolones, tetracycline, aminoglycosides, and sulfonamides, carbapenems, and nitrofurantoin. Type of organisms most common in urine sample were noted, and drugs still effective for the particular organism were noted. Whole of the data were collected and compiled in the year wise manner and compared year wise to see the trend in the resistance pattern. An isolate was considered as MDR if found resistant to three or more antimicrobials belonging to different classes/groups of antimicrobials.[8] C/S reports for other common uropathogens will also be further analyzed.

Statistical analysis

Descriptive statistics was used for analysis. Proportions were used to study the resistance pattern of *Klebsiella* and variables were expressed as percentages. Licensed IBM SPSS statistics version 20 (2011), International Business machines Corp was used for statistical analysis. All the data were expressed as tables and bar diagrams.

RESULTS

Over 3 years period of 2012-2014, a total of 2464 positive urine isolates including 567 *K. pneumoniae* were analyzed. As expected, *Klebsiella. spp*. was the second frequent isolate throughout the 3 years (average of 14% of the total isolates). The next most frequently isolated bacteria were *Proteus mirabilis* (6%), *Pseudomonas aeruginosa* (8%), *Enterococcus faecalis* (2%), and *Streptococcus agalactiae* (1%) with most frequent being *Escherichia coli* (67%). Analysis of the results year wise indicated that the lowest percentage of resistance was manifested against imipenem between 11.94%, 13% and 13.75% for the years 2012-2014, respectively [Table 1]. Resistance to nitrofurantoin is less compared to other drugs over the three consecutive years from 49.03% (2012) to 58.13% (2014). Over the successive years, the resistance to third-generation cephalosporin ceftriaxone tends to increase from 74.95% (2012) to 81% (2014). While resistance to third-generation cephalosporin cefoperazone tends to decrease from 60.19% (2012) to

Table 1: Antibiotic resistance trends of *Klebsiella pneumoniae* isolates for years 2012-2014

Antimicrobial agents	Resistant		
	2012	2013	2014
	Percentage (*n* = 161)	Percentage (*n* = 200)	Percentage (*n* = 206)
Amoxy+clavulanic acid	73.79	84	81.25
Piperacillin+tazobactam	51.46	67	73.13
Aminoglycosides	76.05	77	75.63
Fluoroquinolones	77.77	71.5	68.88
Ceftriaxone	74.95	78.5	81
Cefoperazone+sulbactam	60.19	56.5	49.38
Imipenem	11.94	13	13.75
Nitrofurantoin	49.03	47	58.13
Co-trimoxazole	90.78	95	100
Tetracyline	95.63	100	99.38
Ceftazidime+tazobactum	79.26	78	78.09

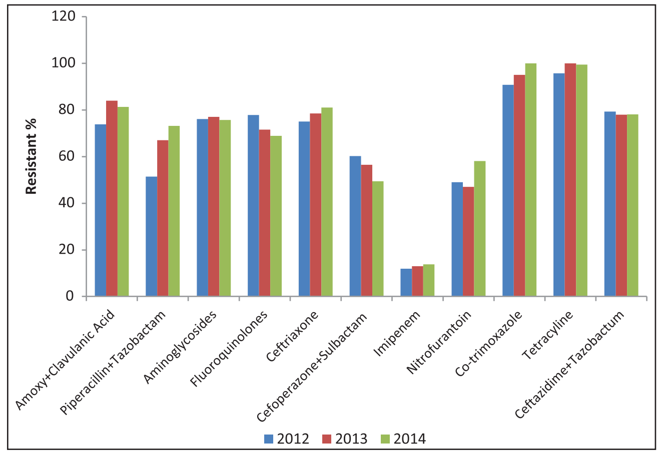

Figure 1: Antibiotic resistance trends of *Klebsiella pneumoniae* isolates in urine samples over last 3 years from 2012 to 2014

49.38% (2014). *Klebsiella* showed absolute resistance (100%) to co-trimoxazole and tetracycline. Two most common classes of drugs used for the treatment of UTIs are fluoroquinolones and aminoglycosides. *Klebsiella* showed the very high amount of resistances on an average of 72.72% and 76.23%, respectively for the two groups over the 3 years [Figure 1].

Multi-drug resistant *Klebsiella pneumoniae*

Those strains which are found to be resistant to three or more than three groups of antimicrobials were taken as MDR strains. While MDR *Klebsiella* percentage resistant to fluoroquinolones, third-generation cephalosporins and aminoglycosides range between 65% (2012) and 67% (2014) over the consecutive years.

DISCUSSION

This study shows the distribution of microbial species and antibiotic resistance patterns of *Klebsiella* pneumonia isolated from North Indian patients with UTI. Rajindra hospital is 1100 bedded hospital located in Patiala, Punjab; it is one of the busiest hospitals in the state. Antibiotic resistance is a major clinical problem in treating infections caused by these microorganisms. The resistance to the antimicrobials has increased over the years. Resistance rates vary from one region to another.[9,10] There are very few studies done in Punjab for keeping a check on the changing trend in antimicrobial resistance.

Gram-negative organisms are the most common organisms causing UTIs. In this study, *E. coli* accounted for approximately 67% of all clinically significant urinary isolates followed by *Klebsiella* (14%), *Proteus spp.* (6%), *P. aeruginosa* (8%), *Enterococcus sp.* (2%), and *S. agalactiae* (1%). The spectrum of uropathogens isolated from urine samples in this study is very similar to the studies done in different regions of India.[11-13] In our study, *Klebsiella spp.* isolates found to be resistant to amoxicillin-clavulanate between 73.05% (2012) and 81.25% (2014). Such high level of resistance of 50% and 76.09% was documented from studies done in Kumar in Bhopal, India and Ullah *et al.* in North West Pakistan respectively.[14,15] Although fluoroquinolones are among the most effective drugs in treating UTI, diverse studies have revealed increasing resistance to fluoroquinolones between 60% and 53%.[15,16] Similarly, in our study resistance to fluoroquinolones is between 77.77% (2012) and 68.88% (2014). This may be due to rampant use of fluoroquinolones as first-line empirical therapy in UTI cases.

Antimicrobials such as piperacillin + tazobactam and aminoglycosides are consistently showing high resistance percentage over the successive 3 years. Third-generation cephalosporins like ceftriaxone is showing a very obvious increasing trend of resistance over the 3 years ranging from 74.95% (2012) to 81 % (2014). In a study done in Bhopal, ceftriaxone resistance is found to be 85 % which is quite similar to our study.[14] This may be due to the increasing clinical use of third-generation cephalosporins following the resistant strains to fluoroquinolones. There is nearly 100% resistance seen with tetracyclines and cotrimoxazole; this is very much similar to a study done in Pakistan (100%).[15] Furthermore, high level of resistance (76%) to co-trimoxazole is reported by a study done in Gwalior India.[17]

Lowest resistance is seen to imipenem and nitrofurantoin in our study. Very low resistance is consistently seen over 3 years, in the case of imipenem 11.94% (2012) and 13.75% (2014). Low resistance to carbapenems may be explained by lesser use of these injectable drugs until date. In a study done by Manikandan in Tamil Nadu, India the results of resistance to imipenem (13.9%) are quite similar to our study.[4] For nitrofurantoin, there is an increasing trend of resistance seen over the three successive years increasing from 49.03% (2012) to 58.13% (2014) which is very similar (53%) to a study done by Sarathbabu *et al*. in Andhra Pradesh, India.[16]

In the present study, another finding which raises an alarm is about MDR, urinary isolates of *Klebsiella spp*. show 65% (2012) and 67% (2014) resistance to fluoroquinolones, third-generation cephalosporins and aminoglycosides collectively. The rising trend of MDR is seen over the successive years. This is comparable to 71.73% MDR *Klebsiella* seen in the study done in done by Ullah *et al*.[15]

In this retrospective study, there is no consideration of patient's demographic data such as age and gender clinical symptoms, complicated versus uncomplicated UTI, which are surely the limitations of this study. On the other hand, the large sample size of UTI patients and comparison of 3 years data are strengths of the study.

CONCLUSION

Our study showed that 67% of *Klebsiella* isolates from urine samples were MDR. Because of this a bacterium resistant to one antibiotic is often much more likely to be resistant to the second choice of antibiotics, thereby increasing the chances of failure of therapy in UTI. This study highlights the problem of very high level of resistance in a small city like Patiala. Antimicrobial resistant patterns are constantly evolving and vary from region to region it is a necessity for constant antimicrobial sensitivity surveillance. This will help clinicians to provide safe and effective empirical therapies with minimal therapeutic failures.

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Conflicts of interest

There are no conflicts of interest.

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