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Antimicrobial susceptibility pattern and ESBL prevalence in *Klebsiella pneumoniae* from urinary tract infections in the North-West of Pakistan

Farhat Ullah[1]*, Salman Akbar Malik[1] and Jawad Ahmed[2]

[1]Department of Biological Sciences Quaid-i-Azam University, Islamabad, Pakistan.
[2]Khyber Medical College, Peshawar, Pakistan.

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Urinary Tract Infections (UTIs) are the most prevalent infections worldwide both in males and females. *Klebsiella* is one of the major pathogens causing UTIs. These bacteria also produce enzymes called Extended Spectrum Beta-Lactamases (ESBL) which render penicillins and cephalosporins inactive. The present study included 92 *Klebsiella pneumoniae*, isolated from urine of patients suffering from UTIs. Antibiotic susceptibility testing and ESBL detection were carried out according to Clinical and Laboratory Standards Institute (CLSI) criteria. Eighteen antibiotics were tested in this study. A total of 54 (58.7%) isolates were found to be ESBL producers. Seventy one percent isolates were resistant to 3 or more antibiotics (Multidrug resistant). Imipenem and meropenem showed high potency with 93.48 and 86.96% isolates being susceptible respectively. Susceptibility to gentamicin was 17.39%; kanamycin 63.04%; gatifloxacin 45.65; ciprofloxacin 41.3%; enoxacin 43.48%; doxycycline 15.22% and to co-trimoxazole only 6.52%. This study reveals that *Klebsiella* isolated from UTI in this region are multi-drug resistant and produce ESBL in large proportions.

Key words: Antibiotic resistance, *Klebsiella pneumoniae*, urinary tract infections, extended spectrum beta lactamase.

INTRODUCTION

Klebsiella species particularly *Klebsiella pneumoniae* are important opportunistic nosocomial pathogens causing a variety of infections including urinary tract infections, pneumonia, septicemia, wound infections and infections in the intensive care units. It has been estimated that *Klebsiella* spp cause 5 - 7% of the total bacterial nosocomial infections (Podschun and Ullmann, 1998). Cephalosporins, fluoroquinolones, aminoglycosides and carbapenems are effective for treating infections caused by *Klebsiella* (Roussel-Delvallez and Wallet, 1998; Lee and Su, 2006; Pound and Fulton, 2007). Resistance has developed to antibiotics in these pathogens (Jain and Mondal, 2007; Landman and Bratu, 2007). Among members of the *Enterobacteriaceae* family, resistance to beta-lactams has been reported to associated with ESBL (Babini and Livermore, 2000), which hydro-lyze oxyimino beta-lactams like cefotaxime, ceftriaxone, ceftazidime and monobactams but have no effect on cephamycins, carbapenems and related compounds (Philippon and Labia, 1989). ESBL positive strains are associated with increased mortality as compared to the ESBL negative strains (Kim and Pai, 2002). Detection of ESBL production is important. One major concern is the spread of ESBL positive bacteria within hospitals, which may lead to outbreaks or to endemic occurrence (Meyer and Urban, 1993; Pena and Pujol, 1998; Lucet and Decre, 1999; Quale and Landman, 2002) . Another concern is failure to treat infections caused by ESBL positive organisms, as therapeutic choices are limited (Paterson and Bonomo, 2005). ESBL producing *Klebsiella* in this part of the world has been observed by several workers; its prevalence reported to be more than 55% (Ali and Raj, 2004; Jain and Mondal, 2007). In a

*Corresponding author. E-mail: farhataziz80@hotmail.com. Tel: 00923339361513

country like Pakistan, where laboratory microbiological diagnosis is not available to eighty percent of the population, the clinicians prescribe more than one antibiotic, which results in increase in antibiotic resistance (Hafiz and Hamedani, 1989). It is necessary to investigate the prevalence of ESBL positive strains in hospitals so as to formulate a policy of empirical therapy in high risk units where infections due to resistant organisms are much higher (Mathur and Kapil, 2002).

MATERIALS AND METHODS

Bacterial isolates

A total of 92 strains of *K. pneumoniae* were collected from Khyber teaching hospital, Peshawar from January 2006 to January, 2007. The samples included urine from hospital patients. The samples received were inoculated onto Blood agar, Cysteine Lactose Electrolyte Deficient (CLED) agar and MacConkey agar (Oxoid, England). After 24 h aerobic incubation at 37°C, isolates were identified to the species level using biochemical tests.

Antimicrobial agents susceptibility testing

Susceptibility to antimicrobial agents was determined by Disc Diffusion method of Kirby Bauer on Muller-Hinton agar (Oxoid, England) as described by the Clinical and Laboratory Standard Institute (CLSI, 2006). The antibiotic discs were obtained from Oxoid, England.

The antibiotics used for antibiogram determination of the collected strains were: ampicillin (AMP), amoxicillin+ clavulanic acid (AMC), cephradine (CE), cefaclor (CEC), ceftrixone (CRO), ceftazidime (CAZ), cefpirome (CPO), cefoperazone+sulbactam (SCF), piperacillin+tazobactam (TZP), meropenem (MEM), imipenem (IPM), doxycycline (DO), ciprofloxacin (CIP), gatifloxacin (GTX), enoxacin (ENX), gentamicin (CN), amikacin (AK) and co-trimoxazole (SXT). *E. coli* NCTC 10418 was used as control for susceptibility testing.

Detection of extended spectrum beta lactamases (ESBL)

The initial screening and phenotypic confirmatory tests recommended by the CLSI for ESBL detection were carried to assess the prevalence of ESBL (CLSI, 2006). In the initial screening test a disc of amoxycillin+clavulanic acid (20 + 10 ug) was placed in centre of the Petri plate already inoculated with the test organism while aztreonam (30 ug) cefotaxime (30 ug) ceftazidime (30 ug) cefpodoxime (30 ug) and ceftriaxone (30 ug) discs were placed at a distance of 20 - 25 mm (centre to centre) from the amoxycillin+ clavulanic acid disc on the same plate. Zones of inhibition around the third generation cephalosporin discs and aztreonam were observed after 18 h incubation at 37°C. If the zone of inhibition around one or more cephalosporin discs and aztreonam was extended on the side nearest to the amoxycillin+clavulanic acid, the organism showing this synergy was labeled as ESBL positive. In the phenotypic confirmatory test, the test organisms were grown on Muller-Hinton agar and discs of cefotaxime (30 ug) and ceftazidime (30 ug) separately and each of these in combination with clavulanic acid (10 ug) were placed on the surface of the lawn of bacteria. A difference of 5 mm between the zone of inhibition of a single disc and in combination with clavulanic acid was considered as ESBL positive isolate. *E. coli* NCTC 10418 was used as ESBL negative control and *K. pneumoniae* ATCC 700603 was used as ESBL positive control strain.

RESULTS

A total of 92 isolates of *K. pneumoniae* were obtained from urine samples submitted to the microbiology laboratory in Khyber Teaching Hospital, Peshawar. Age range of patients was between 1 and 60 years with a mean of 25.28 years. More isolates were recovered from females (56) as compared to males (36).

Among the beta-lactams tested, the most effective antibiotics were carbapenems (meropenem and imipenem). Meropenem had 93.48% activity and imipenem had 86.96% activity. These were followed by ceftriaxone having 32.61% activity, cefpirome 30.43%, ceftazidime 28.26%, cefeclor 19.57%, cephradine 15.22% and ampicillin had 13.04% activity. Susceptibility data of the isolates is given in Table 1. Susceptibility results of combination of beta-lactams and beta-lactamase inhibitors tested were: cefoperazone+sulbactam 63.04% susceptibility, piperacillin+tazobactam 45.65% susceptibility and amoxicillin+clavulanic had acid 17.39% had susceptibility. A total of 58 (63.04%) isolates were susceptible to amikacin and 16 (17.39%) to gentamicin. Ciprofloxacin had maximum activity (45.65%) among fluoroquinolones against the isolated *Klebsiella*, followed by enoxacin (43.48%) and gatifloxacin (41.3%). Doxycycline had 15.22% activity and co-trimoxazole had 6.52% activity.

Among the 6 strains resistant to both imipenem and meropenem, 4 (66.67%) were susceptible to amikacin. Among the 30 isolates resistant to amikacin, 28 (93.33%) were susceptible to imipenem and 26 (86.67%) to meropenem. A total of 39 strains were resistant to all the fluoroquinolones used. Thirty four among this fluoroquinolone resistant *K. pneumonia* were sensitive to impenem and meropenem.

Gentamicin resistant isolates were generally co-resistant to co-trimoxazole (100%), doxycycline (89.19%), ciprofloxacin 59.46% and ceftazidime 51.35%, however, resistance among such strains to imipenem and meropenem was much lower being 10.81 and 8.11% respectively. A total of 66 (71.73%) isolates were multidrug resistant (MDR) (resistant to 3 or more drug classes). The most prevalent MDR pattern was resistance to beta-lactams, doxycycline, fluoroquinolones, aminoglycosides and co-trimoxazole.

In this study 54 (58.70%) *K. pneumoniae* were found to be ESBL producers, 30 (55.56%) isolated from females and 24 (44.44%) isolated from males. Resistance was high in the ESBL positive strains as compared to the ESBL negative strains. A statistically significant difference was found in the susceptibilities of flouroquino-lones (CIP, ENX, GTX), amikacin, cefoperazone/ sulbactam, piperacillin/tazobactam, and meropenem for ESBL positive and ESBL negative isolates (p value < 0.05). Resistance to imipenem, doxycycline, gentamicin and sulphamethoxazole+trimethoprim was slightly high in ESBL positive isolates as compared to ESBL negative ones but it was not statistically significant (p value > 0.05) (Table 2).

Table 1. Antibiotic susceptibility of the isolated *Klebsiella pneumonia* (n = 92).

Antibiotic	Resistant number (%)	Intermediate number (%)	Susceptible number (%)
AMP	46 (100.0)	00 (00.00)	00 (00.00)
AMC	35 (76.09)	03 (06.52)	08 (17.39)
CE	37 (80.43)	02 (04.35)	07 (15.22)
CEC	37 (80.43)	00 (00.00)	09 (19.57)
CRO	25 (54.35)	06 (13.04)	15 (32.61)
CAZ	25 (54.35)	08 (17.39)	13 (28.26)
CPO	31 (67.39)	02 (04.39)	14 (30.43)
SCF	02 (04.35)	15 (32.61)	29 (63.04)
TZP	18 (39.13)	07 (15.22)	21 (45.65)
MEM	03 (06.52)	01 (02.17)	43 (93.48)
IPM	06 (13.04)	00 (00.00)	40 (86.96)
CIP	24 (52.17)	03 (06.52)	19 (41.30)
GTX	23 (50.00)	02 (04.35)	21 (45.65)
ENX	25 (54.35)	01 (02.17)	20 (43.48)
CN	37 (80.43)	01 (02.17)	08 (17.39)
AK	15 (32.61)	02 (04.35)	29 (63.04)
DO	38 (82.61)	01 (02.17)	07 (15.22)
SXT	43 (93.48)	00 (00.00)	03 (06.52)

Table 2. Comparison of susceptibility to antimicrobial agents tested between ESBL positive and ESBL negative *K. pneumoniae* isolates (n = 92).

	ESBL +ve n = 54			ESBL -ve n = 38		
Antibiotic	Resistant number (%)	Intermediate number (%)	Sensitive number (%)	Resistant number (%)	Intermediate number (%)	Sensitive number (%)
GTX	36 (66.67)	00 (00.00)	18 (33.33)	10 (26.32)	04 (10.53)	24 (63.16)
CIP	40 (74.07)	00 (00.00)	14 (25.93)	08 (21.05)	06 (15.79)	24 (63.16)
ENX	38 (70.37)	00 (00.00)	16 (29.63)	12 (31.58)	02 (05.26)	24 (63.16)
CN	40 (74.07)	02 (03.70)	12 (22.22)	34 (89.47)	00 (00.00)	04 (10.53)
AK	28 (51.85)	00 (00.00)	26 (48.15)	02 (05.26)	04 (10.53)	32 (84.21)
DO	44 (81.48)	00 (00.00)	10 (18.52)	32 (84.21)	02 (05.26)	04 (10.53)
SXT	52 (96.30)	00 (00.00)	02 (03.70)	34 (89.47)	00 (00.00)	04 (10.53)
SCF	02 (03.70)	26 (48.15)	26 (48.15)	02 (05.26)	04 (10.53)	32 (84.21)
TZP	32 (59.26)	12 (22.22)	10 (18.52)	04 (10.53)	02 (05.26)	32 (84.21)
MEM	06 (11.11)	02 (03.70)	46 (85.18)	00 (00.00)	00 (00.00)	38 (100.0)
IPM	10 (18.52)	00 (00.00)	44 (81.48)	02 (05.26)	00 (00.00)	36 (94.74)

DISCUSSION

This data obtained from clinical samples of *K. pneumoniae*, shows high antibiotic resistance. Worldwide resistance to antibiotics has increased in *Klebsiella* (Tonkic and Goic-Barisic, 2005).

Carbapenems are the drugs of choice for many infections caused by gram positive and gram negative bacteria (Nicolau, 2008; Shah, 2008). Carbapenems were found to be the most effective antibiotics, 93.48 and 86.96% isolates being susceptible to meropenem and imipenem respectively. This is consistent with findings of Al-Zahrani and Akhtar from Saudi Arabia (Al-zahrani and Akhtar, 2005).

Penicillins are bactericidal; inhibit bacterial cell wall synthesis (Trevor and Katzung, 2001). Resistance to ampicillin is high in *Klebsiella*. We recorded 100% isolates resistant to ampicillin. This is in agreement with other studies (Aktas and Yigit, 2002; Orrett, 2005).

Cephalosporins, particularly second and third generation cephalosporins have been used for *Klebsiella* infections (Jett and Ritchie, 1995). In our study, 67.39% isolates were resistant to the fourth generation cephalosporin (cefpirome). Tuchilus and Poiata from Romania in

2006 have reported 40% resistance in *Klebsiella* to cefpirome (Tuchilus and Poiata, 2006). A total of 54.35% isolates were resistant to the third generation cephalosporins (ceftazidime and cefotaxime) and 80.43% were resistant to the second and first generation cephalosporins (cefaclor and cephradine) . Singh and Goyal (2003) from India have recorded 84% resistance to cefotaxime.

Aminoglycosides have good activity against clinically important gram negative bacilli (Gonzalez and Spencer, 1998). Amikacin showed good activity with 63.04% isolates being susceptible and 17.39% isolates were susceptible to gentamicin. Revathi and Puri, from India have reported 39.10% activity of amikacin and 16.70% activity of gentamicin in *Klebsiella* (Revathi and Puri, 1998). This may be due to increased use of amikacin and gentamicin in India and as compared to Pakistan. According to Miller and Sabatelli, (1997), pattern of resistance to aminoglycosides is affected by selective pressure in different regions (Miller and Sabatelli, 1997).

The observed resistance in *Klebsiella* to ciprofloxacin was 52.17%. This is lower than studies conducted in India (Revathi and Puri, 1998; Singh and Goyal, 2003) and higher than those of USA (Fedler and Biedenbach, 2006). Half of the isolates were resistant to gatifloxacin. This is in contrast to data from USA, where a much lower resistance was recorded to gatifloxacin in *Klebsiella* that is 1.8% only (Fedler and Biedenbach, 2006). Doxycycline and co-trimoxazole have been used for infections caused by *Klebsiella* (Digranes and Solberg 1980; Bauernfeind and Horl, 1987). We recorded 82% resistance to doxycycline and 93% to co-trimoxazole.

Multi-drug resistance (MDR) is a major problem in the management of uropathogens (Tankhiwale and Jalgaonkar, 2004; Akram and Shahid, 2007; Hasan and Nair, 2007). Generally, pathogens in hospitals are resistant to multiple antibiotics due to increased selection pressure of antibiotics (Gold and Moellering, 1996). This MDR may be due to plasmids harboring several resistance genes which are transferred from one bacterium to another (Ram and Gupta, 2000). Mathai and Grape (2004) have linked such resistance pattern to the presence of integrons (Mathai and Grape 2004). Multidrug Resistance (MDR) in *Klebsiella* is increasing throughout the world (Subha and Ananthan, 2001; Tokatlidou and Tsivitanidou, 2008). We found 66 (71.73%) isolates as MDR. This is in contrast to Subha and Ananthan from India. They have reported 100% multidrug resistance in *Klebsiella* in 2002.

Extended Spectrum Beta-Lactamases producing strains are mostly associated with UTIs (Melzer and Petersen, 2007) . The mortality rate, length of hospital stay and cost of hospitalization due to infections caused by ESBL producing *Klebsiella* isolates is significantly higher than caused by ESBL non-producers *Klebsiella* (Schwaber and Navon-Venezia 2006; Melzer and Petersen, 2007). Extended-spectrum beta-lactamase (ESBL) producing strains of *K. pneumoniae* have caused major therapeutic problems worldwide since the majority are resistant to various antibiotics (Feizabadi and Etermadi, 2006) . ESBL prevalence varies in different countries. ESBL prevalence of 44.5%, 58% and 39.5% has been reported in *E. coli* from Iran, India and Bangladesh respectively (Rahman and Haq, 2004; Feizabadi and Etemadi, 2006; Jain and Mondal, 2008). In our study, we found 54 (58.5%) isolates as ESBL producers. This is higher than reported by others from Pakistan (Jabeen and Zafar, 2005).

Further studies are required to investigate MDR, ESBL from other parts of Pakistan using more isolates. Studies of molecular epidemiology of these resistance genes can also be used for comparison with genes already isolated from other parts of the world.

This study shows that *K. pneumoniae* recovered from clinical specimens in this region produce ESBL in much high number. Thus, are resistant to penicillins and cephalosporins, which are important drugs for the treatment of UTIs. Such isolates are also resistant to flouroquinolones, aminoglycosides, tetracyclines and co-trimoxazole. Carbapenems are the drugs of choice against such infectionss caused by *Klebsiella*. The higher MDR in this region is a cause for concern. Further molecular studies should be conducted to know the basis of this MDR. Strict antibiotic policy should be adopted in hospitals to estimate the impact of higher resistance in bacteria and to take steps for reducing this resistance.

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