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Full Length Research Paper

High prevalence of multi-drug- resistance (MDR) and extended spectrum β-lactamases (ESBL) producing bacteria among community-acquired urinary tract infections (CAUTI)

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Urinary tract infection (UTI) remains to be the most common infection diagnosed in outpatients as well as in hospitalized patients. Appropriate knowledge on the current antimicrobial susceptibility pattern of uropathogen is essential for appropriate therapy. Thus, a prospective study was carried out in the Government Medical College and Hospital at Anantapur, India from July - December, 2007 in order to determine the frequency of multidrug resistance (MDR) and Extended-spectrum β-lactamase (ESBL) producing uropathogens from community acquired urinary tract infection (CAUTI). Of the 410 samples tested in this study, 222 isolates showed significant bacterial growth among which Escherichia coli strains was most prevalent (45%) followed by Klebsiella spp (18%). Among gram negative bacterial isolates, high prevalence of antibiotic resistance was observed against Ampicillin, Norfloxacillin and Co-trimoxazole. 26% of strain included in this study was found to be ESBL producer where MDR is higher compare to non ESBL producer. Moreover Imipenem showed a high potency and widest coverage against gram negative isolates (100%). This presented study showed a high frequency of antimicrobial resistance and ESBL production in Enterobacteriaceae isolated from CAUTI patients in India.

Key words: Prevalence, UTI, multidrug resistance, ESBL.

INTRODUCTION

In spite of the wide spread availability of antibiotics, urinary tract infection (UTI) remains to be one of the most common infectious diseases diagnosed in out patients (Gales et al., 2000). It is estimated that 150 million urinary tract infections occur annually world wide (Stamm and Norrby, 2001).Urinary tract infections are the most common bacterial infections in women and results in a significant morbidity and health care costs (Harding and Ronald, 1994). *Escherichia coli* is the primary urinary tract infection pathogen isolated from outpatients (Nicolle, 2001) while *Klebsiella* spp and *Staphylococcus* are less common pathogens.

Usually antibiotics are given empirically before the laboratory results of urine culture are available to ensure appropriate therapy. However resistance to commonly-prescribed antibiotics is an expanding global health problem and various studies clearly demonstrated increasing antibiotic resistance in uropathogens causing both community- and nosocomially acquired UTIs (Farrar, 1985; Tenvor and Hughes, 1996; Rahal et al., 1997; Finch, 1998). Therefore, it is recommended for physicians to obtain information about the local resistant rate as stated by the Infectious Disease Society of America (Warren et al., 1999). In addition, surveillance at the institutional and regional level is required to monitor changes in susceptibility of uropathogens. Current knowledge of the organisms that cause urinary tract infection is mandatory (Gruneberg, 1982) and the detection of antibiotic resistance and ESBL producer may facilitate the imple-

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mentation of effective therapy and control measures. Infection due to ESBLs producers range from uncomplicated UTI to life threatening sepsis.

The present study was carried out to determine institutional *in vitro* antibiotic susceptibility pattern and detection of extended spectrum β-lactatamases (ESBL) producers in a population of different uropathogens isolated from a total of 410 patients over a period of six months in the Department of Microbiology, Government Medical College and Hospital, Anantapur, India.

MATERIALS AND METHODS

Collection of urine samples

During the July - December, 2007 a total 410 urine samples were received in the Department of Microbiology, Government Medical College and Hospital, Anantapur. From these urine specimens of symptomatic UTI patients 235 bacterial isolates were identified by conventional methods (Koneman EW, 1997.)

Collection method

While collecting urine for culture, care should be taken to avoid contamination with normal flora of the anterior urethra or perineal skin. The common method of collection is midstream clean catch. This cannot be done properly in infants who do not have proper control of micturition or have a nonretractable prepuce. In such infants and children suprapubic aspiration is recommended.

Isolation and identification of bacteria

Culture was isolated by the calibrated loop technique; 0.001 ml of urine sample was plated on Cysteine –Lactose –Electrolyte Deficient (CLED) medium and blood agar media plates and incubated at 37°C overnight in incubator. After incubation the cultures developed on media were observed and the colonies were counted by quibey colony counter. The bacterial isolates were identified based on the colony morphology and biochemical reactions followed by the standard methods (Myers and Koshi, 1982) The antibiotic sensitivity of the organism was performed by modified stokes disk diffusion method on Muller-Hinton agar plates (Agarwal, 1974).

The antibiotic susceptibility test

The antibiotic sensitivity of the organism was performed by modified stokes disk diffusion method on Muller-Hinton agar plates (Agarwal, 1974) as described by the National Committee for Clinical Laboratory Standards (presently called as Clinical Laboratory Standard Institute). The antibiotic disks were obtained from Hi Media, India. Antibiotic discs such as third generation cephalosporin (3GC) Viz Cefotaxime (30 mg), Cetazidime (30 mg) Ceftriaxone (30 mg), and other antibiotics like Gentamycin (10 mg), Amikacin (10 mg), Nalidixic acid (30 mg), Norfloxacin (10 mg), Ciprofloxacin (5 mg), Aminopenicilin and Pipercillin (100 mg), Tetracycline (30 mg), Trimethoprim-Sulfamethoxozole (25 mg), and Nitrofurantoin (300 mg), were used. E. coli ATCC 25922 strain, S. aureus ATCC 29213strain, and P. aeruginosa ATCC 27853 strains were used as quality control strains. Interpretative criteria for each antimicrobial tested were those recommended by the NCCLS-2000.

ESBL screening and detection

The ESBL screening was done in accordance with the criteria recommended by the Clinical Laboratory Standards Institute CLSI 2005 (Formerly NCCLS). An inhibition zone of ≤ 27 mm for cefotaxime and ≤ 22 mm for ceftazidime indicated that the isolated strain probably ESBL producer. ESBL detection was performed as recommended by NCCLS confirmatory procedure using cefotaxime (30 µg) and ceftazidime (30 µg) discs alone and in combination with clavulanic acid. MICs were determined for cefotaxime and ceftazidime with and without the presence of clavulanic acid by agar dilution techniques on Mueller-Hinton agar and results are interpreted according to (NCCLS criteria2000). E. coli ATCC 25922 strain (β-lactamase negative) and K. pneumoniae ATCC 700603 (ESBL positive) strain were used as controls through out the study.

Confirmation of ESBL by e-test

The confirmation of ESBL was also performed by E-test ESBL strips (AB Biodisc, Solna, Sweden), and the test was performed in accordance to the manufacturer's instructions. Double-ended strips containing gradient of cefotaxime (CT) or ceftazidime (TZ) at one end and cefotaxime or ceftazidime plus clavulanic acid (CTL and TZL) at the other end were tested in parallel. The presence of ESBL was confirmed by the appearance of phantom zone below CT or deformation of TZ inhibition ellipse or when clavulanate caused a more than or equal to three doubling concentration decrease (ratio of ≥8) in the MIC values of cefotaxime and ceftazidime.

RESULTS

Of the 410 urine samples processed, 222 (54%) gave significant growth of pathogens. It was observed that more organisms were isolated from adult women (68.4%) compare to those from men (31.5%). Of the 222 bacterial isolates from urine cultures, gram negative aerobic rods accounted for (77%) while gram positive cocci accounted for the rest (23%). The total pathogens isolated and recovered are distributed as the following; *E. coli* (44.5%), *K. pneumoniae* (18.4%), *Proteus* spp (6.7%) *Citrobacter* spp (2.7%) *Pseudomonas* spp (4.5%), *Staphylococcus aureus* (11.2%), Coagulase negative *Staphylococcus* (7.6%), Enterococcus spp (2.7%) and *Streptococcus agalactaceae* (1.3%); as summarized in Table 1.

The antimicrobial susceptibility pattern of 13 selected antimicrobial agents of different classes against the most frequent gram negative aerobic urinary tract infection pathogens are summarized in Table 2. The drug resistance pattern of the *E. coli* and *Klebsiella* isolates showed high rate of resistance against 3GC antibiotics (ceftazidime, cefotaxime, ceftriaxone), followed by Ampicillin, ciprofloxacin, and co-trimoxozole. The antibiogram revealed that a majority of isolates of *E. coli* and *Klebsiella* were found to be resistant to at least one 3GC antibiotics used in the study. E. coli isolates showed high resistance against Ampicillin (81%), Co-Trimoxozole (70%), Nalidixic acid (61%) Cephotoxime (58%) and Ceftriaxone (54%) were found, indicating maximum resistance to these drugs respectively. *Klebsiella* isolates showed resistance against Ampicillin (72%), Norfloxacilin

Table 1. Bacterial isolates from urinary tract infections**.**

Microorganisms	No. of isolates and percentage (%)		
	Women	**Men**	**Total**
Escherichia coli	72 (47.3)	27 (38.5)	99 (45)
Klebsiella pneumoniae	28 (18.4)	13 (18.5)	41(18.4)
Proteus mirabilis	8 (4.3)	4 (5.7)	12 (5.4)
Citrobacter spp.	4 (2.6)	2 (2.8)	6 (2.7)
Proteus vulgaris	2 (1.3)	1 (1.4)	3 (1.3)
Pseudomonas aeruginosa	7 (4.6)	3 (4.2)	10 (4.5)
Staphylococcus aureus	15 (9.8)	10 (14.2)	25 (11.2)
Coagulase negative *staphylococcus*	10 (6.5)	7 (10)	17 (7.6)
Enterococcus faecalis	4 (2.6)	2 (2.8)	6 (2.7)
Streptococcus agalactaceae	2 (1.3)	1 (1.4)	3 (1.3)
Total	152 (100)	70 (100)	222 (100)

Table 2. Common Antimicrobial resistance pattern in gram - negative bacilli.

Antibiotics	Percent of isolates resistance to antibiotics				
	Escherichia coli **(n = 99)**	***Klebsiella pneumoniae*** **(n = 41)**	***Proteus*** **spp. (n = 15)**	***Citrobacter*** **spp. (n = 06)**	***Pseudomonas aeruginosa*** **(n = 10)**
AM	81.0	72.0	59.0	49.0	62.0
CF	44.0	49.0	53.0	52.0	71.0
CE	58.0	53.0	39.0	43.0	58.0
G	28.0	31.0	30.0	37.0	36.0
TB	5.0	12.0	22.0	28.0	28.0
AK	12.0	25.0	24.0	26.0	21.0
NF	62.0	57.0	67.0	57.0	61.0
C	43.0	46.0	62.0	48.0	53.0
TET	61.0	52.0	49.0	53.0	49.0
NA	69.0	44.0	61.0	48.0	68.0
CT	70.0	50.0	57.0	54.0	70.0
Ci	54.0	49.0	42.0	38.0	40.0
IM	00.0	00.0	00.0	00.0	00.0

AM=Ampicilin, CF=Ciprofloxacin, CE=Cefotaxime, G=Gentamicin, TB=Tobramycin, AK=Amikacin, NF=Norfloxacin, C=Chloromphenicol, TET=Tetracyclin, NA=Nalidixic acid, CT=Co-trimoxozole, Ci=Ceftriaxone. IM=Imipenem.

(57%), Cefotaxime (53%), Co-Trimoxozole (50%), and Ceftriaxone (49%). Among the 222 isolates that were tested in this study, gram positive pathogens accounted for only 23% of the total bacterial isolates. The antimicrobial potency of 13 selected drug and the most frequent gram positive UTI pathogens are presented in Table 3.

A total of (26.3%) isolates were found to be ESBL producer as detected by NCCLS method. High prevalence rate of ESBL producing stains have been reported in Klebsiella (34.1%) while similar percentage was observed in E. coli strains (30.3%). Other isolates tested in this study have less prevalence rate of ESBL producing strain compare to either *E. coli* or *Klebsiella,* as summarized in Table 4.

DISCUSSION

This study described the susceptibility pattern and distribution of ESBL among 222 bacterial pathogens isolated from urine cultures, collected from July to December, 2007 in the Government Medical College and Hospital, Anantapur, India. The majority of these uropathogens were isolated from adult female (67.6%), which correlates with previously shown data that reported urinary tract infections are far more common in women than men (Foxman, 2002). out of the uropathogens tested

Table 3. Common Antimicrobial resistance pattern in gram – positive bacilli.

Antibiotics	Percent of isolates resistance to antibiotics			
	Staphylococcus aureus (n=25)	Coagulase negative *staphylococcus* (n=17)	*Enterococcus* spp (n=6)	*Streptococcus agalacteciae* (n=3)
P	72.0	59.0	15.0	13.0
KA	36.0	28.0	28.0	23.0
TB	21.0	19.0	13.0	15.0
ERX	28.0	27.0	23.0	28.0
C	22.0	31.0	24.0	32.0
G	26.0	23.0	15.0	18.0
AK	27.0	19.0	19.0	12.0
AC	38.0	31.0	30.0	29.0
CF	25.0	38.0	32.0	31.0
NA	40.0	36.0	37.0	27.0
CT	39.0	29.0	24.0	32.0
M	16.0	13.0	ND	ND

AM=Ampicillin, CF=Ciprofloxacin, GEN=Gentamicin, TB=Tobramycin, K=Amikacin, C=Chloromphenicol, NA=Nalidixicacid, CT=Cotromoxozole, Ci=Ceftriaxone. M=Methicillin, P=Penicillin, ERX=Erythromycin, KA=Kanamycin, AC=Amoxyclav, ND=Not determine.

Table 4. The species distribution of Extended Spectrum β-lactamases (ESBL) producing organisms.

Organisms	No. of isolates	No. of ESBL	ESBL (%)
Escherichia coli	99	30	(30.3)
Klebsiella pneumoniae	41	14	(34.1)
Citrobacter spp.	6	1	(16)
Proteus spp.	15	-	-
Pseudomonas aeruginosa	10	-	-
Total	171	45	(26.3)

in this study, gram negative rods accounted (77%) predominately for *E. coli* and *Klebsiella* spp. The presented data showed that *E coli* strains represent approximately 45% of the bacterial strains isolated from patients with community acquired UTI. *Klebsiella* spp. were less common among community acquired UTI with 41 isolates representing (18.4%). This is consistent with other reported studies in different parts of the world (Gupta et al., 2002; Akata et al., 2003; Matute et al., 2004; Manges et al., 2006; Akram et al., 2007).

Our data demonstrated that *E. coli* and *Klebsiella* isolates are highly resistant to Ampicilin (81 and 72%) respectively. These findings support previous findings of Indian isolates being more resistant to Ampicilin compared to those of USA, Europe, and Latin America (Vormen et al., 1999; Kahlmeter, 2003; Andrade et al., 2006). In this study E coli isolates were most commonly resistant to Ampicilin, Co-trimoxozole, and Nalidixic acid followed by the Norfloxacin, Tetracyclin, and Cefotaxime. On the other hand Imipenem (100%), Tobramycin (95%), and Amikacin (88%) have a high potency against *E. coli* isolates as well as other gram negative uropathogens tested in this study. Similar antibiotic susceptibility pattern was observed with other gram negative microorganisms including *Klebsiella* spp., *Proteus* spp., *Citrobacter* spp., and *Pseudomonas aeruginosa* (Table 2) which goes consistently with other reports (Baby padmini and Appla raju, 2004; Woodford et al., 2004; Pitout et al., 2004; Pournaras et al., 2004; Brigante et al., 2005).

Gram positive cocci accounted for 23% of the uropathogens tested in this study, with *Staphylococcus* spp. being predominant. It was found that the antibiotic resistant pattern of the gram positive cocci is less than that of gram negative pathogens. Resistance to Penicillin was most common in *Staphylococcus* spp. β-lactam drugs are commonly included in the empirical antibiotics treatment of gram negative pathogens, however ESBL producing bacteria may not be susceptible to such treatment. These findings showed that 26.4% of UTI pathogens tested were ESBL producing strains out of them 34.1% were Klebsiella spp., 30.3% were E. coli and 16% were Citrobacter spp. The high prevalence rate of ESBL producing strains have been previously reported in a number of studies (Gupta et al., 2002; Akata et al., 2003; Akram et al., 2007). A 30.3% of E. coli isolates were ESBL producers, which is higher than reported figures in Canada (2.7 - 6.2%) and USA (2.2 - 6.6%) and is lower than those reported in India (41 - 40%) (Baby padmini and Appla raju, 2004).

Conclusion

The findings of this study demonstrated an increase in the prevalence of resistance to a number of used antimicrobial agents up to alarming levels. Many isolates were found resistant at least 3 antibiotics. This increased rate is an expanding global health crisis that threatens the live of many individuals. In view of the emerging drug resistance amongst bacterial therapy should only be advocated, as far as possible after culture and sensitivity has been performed and hence it is suggesting that routine diagnosis of ESBL producing strains should be done, this would not only help in the proper treatment of the patient but also prevent further development of bacterial drug resistance. Monitoring of ESBL production and antibiotic susceptibility testing were mandatory to improve the empirical treatment.

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