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Full Length Research Paper

Patterns of antibiotic sensitivity of bacterial pathogens among urinary tract infections (UTI) patients in a Pakistani population

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Urinary tract infections (UTI) are common and frequently encountered serious morbidity that afflicts its toll not only to all segments of human population but also results in increasing antibiotic resistance due to persistence and mis-management of the ailment. Pathogenic organisms' isolation and determination of antibiotic resistance by bacterial uropathogens in a cross section of patients was investigated at National Institute of Health, Islamabad. A total of 115 samples were collected from June to the August 2009. Identification was conducted by conventional biochemical tests and API 20E system. Percentage identification of API-20E was 100% for *Enterobacter cloacae and Klebsiella pneumoniaea* while 98.9% for *E. coli.* Antibiotic sensitivity test was analyzed by disc diffusion method using different antibiotics and their zone of inhibition was measured. The bacterial isolates were identified as *Escherichia coli* (46.98 %) and *E. cloacae,* methicilline resistant *Staphylococcus aureus* (MRSA)*, Staphylococcus saprophyticus* (1.20 %). In this study it was found that *K. pneumoniae* showed highest sensitivity (80%) to cefapime and low susceptibility (13%) to ciprofloxacin, while the highest resistance (60%) to gentamicin and the lowest (6%) to meropenem, nitrofurantoin and ciprofloxacin was also observed. The susceptibility of *S. aureus* was highest (64%) to amikacin, augmentin and oxacillin and lower sensitivity for ampicillin and moderate for erythromycin, methicillin, and cefotaxime with 45% outcome. The overall results obtained indicated varied patterns of antibiotic sensitivity and resistance, warranting therefore the judicious and rational use of antibiotic in the routine treatment of UTIs to prevent the recurrence as well as resistant strains.

Key words: Urinary tract infection (UTI), antimicrobial sensitivity, disc diffusion, analytical profile index (API 20E), uropathogens.

INTRODUCTION

Urinary tract infection (UTI) is a serious health problem and it has been estimated that about six million patients visit outpatient departments and about 300,000 are treated in the wards every year for UTI worldwide (Akortha and Ibadin, 2008). With the constantly shifting trends in drug resistance, antibiotic options, and pharmacoeconomic considerations, urinary tract infections (UTIs) continue as one of the most frequently diagnosed cases, having an estimated figure of 150 million per annum worldwide. In fact, UTIs are the leading cause of Gram-negative bacteremia in patients of all ages and are associated with a high risk of morbidity and mortality, especially in the elderly, and account for significant health care costs (Azra et al., 2007; Ahmadzadeh and Askarpour, 2007).

Urinary tract infection (UTI) could be defined as the persistent presence within the urinary tract of actively

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Figure 1. Kirby-buyer method of antibiotic sensitivity test. Circles indicate the inhibition zones of different antibiotic discs where different digits indicate the different antibiotics.

multiplying microorganisms. UTI implies both microbial colonization of the urine and invasion of the lower or upper urinary tract by microorganisms (Ali, 2000).

The traditional guideline that the urine containing more than 100, 000 bacteria/ ml for an incidence of UTI have been modified currently. Count as low as 1000 /ml of any single bacterial type, or as few as 100 /ml of coliforms such as *E. coli*, are now considered an indication of significant infection, especially if leukocytes appear in the urine (Adeleke and Asani, 2009; Biyikli et al., 2004).

Microorganisms that cause UTIs almost come from the skin at or near the opening of the urethra. Uropathogens differ in terms of the virulence factors and pathogenic mechanisms that allow them to colonize and infect the urinary tract. Gram negative bacteria cause 80-85% where as Gram positives cause 15-20% of the cases. Common Gram-negative species include *E. coli*, *Klebsiella*, *Proteus*, *Enterobacter*, *Pseudomonas*, and *Serratia* spp. and Gram-positive organisms, including group B streptococci, *Enterococcus* sp., and *Staphylococcus aureus* and *Staphylococcus saprophyticus*, have also been frequently isolated (Bakhsh et al., 2006; Bajaj et al., 1999; Davidson's, 1999; Ehinmidu, 2003; Elder et al., 2004).

The incidence of UTI is greater in women (20%) as compared to men that may be either due to anatomical predisposition or urothelial mucosa adherence to the mucopolysaccharide lining or other host factors and vice versa for infants due to higher incidences of obstructive anomalies of urinary tract in boys than in girls. In children approximately 5% of girls and 1% of boys have a UTI by 11 years of age, in the neonates is 0.01-1% and can also be as high as 10% in low birth weight and preterm babies (Foxman, 2003; Gales et al., 2002; Guidoni et al., 2008; Gupta et al., 1999; Howes, 2005).

The World Health Organization (WHO) has called antibiotic resistance an emerging disease. Bacteria may be innately resistant or may acquire resistance to antibiotics. The rapid spread of bacterial resistance to antimicrobial agents has led to the search for newer and more potent drugs. However, as soon as the new drugs appear, rational use of antibiotics can effectively overcome the problem of bacterial resistance. An extensive body of clinical research confirms that the fluoroquinolones are extremely effective for the treatment of UTIs ranging in severity from uncomplicated cystitis to urosepsis. The superiority of ciprofloxacin compared to trimethoprim-sulfamethoxazole has also been confirmed in patients with acute pyelonephritis. The Ampicillin and Nitrofurantoin have also been recommended to treat UTIs in routine (Iqbal et al., 1997; Jamieson et al., 2006; Jenson and Baltimore, 2006).

The present study was aimed at evaluation of the patterns of antibiotics sensitivity against uropathogens in different group ages of both genders. For this purpose samples were collected in summer session from patients suspected with urinary tract infection (UTI), attending the Microbiology laboratory of the Public Health division, National Institute of Health (NIH), Islamabad, Pakistan.

MATERIALS AND METHODS

Sampling and Isolation

For the purpose of this study about 115 clean catch specimens of Midstream urine (MSU) were collected using standard methodology as explained by Monica cheebrough laboratory practice manual.

After inoculation on CLED (Cystien Lactose Electrolite Deficient), Blood agar and MacConkey agar for an overnight incubation the specimens were analyzed for uropathogens as follows:

Examination of *E. coli*

For examination of E. coli, after overnight incubation, the colony forming unit (cfu) was performed. The samples showing number of colonies > 10^5 was considered as pathogenic count for *E coli*. It was also considered as significant bacteriuria and the isolates were subjected to further antibiogram analysis. If the colony forming unit (cfu) remained less than 10^5, it was considered as non–significant growth in case of *E. coli* or negative sample.

Examination of other bacterial pathogens

This examination was made on the basis of cultural characteristics, morphology, Gram reactions and biochemical characteristics. When confirmation was specifically needed in case of Gram negative microorganism of *Enterobacteriaceae* family, the API20E (Biomerieux) kit was also used.

Once identified, the samples positive for Gram negative bacteria, and Gram positive bacteria were then further tested for antimicrobial susceptibility using Kirby Bauer method on Muller Hinton agar. The inhibition zones were measure in mm as shown in Figure 1.

Table 1. The distribution of UTI patients in relation to their age group

S/N	Age group (years)	No. of males	No. of females
1	1-10	2	10
2	11-20	5	10
3	21-30	7	20
4	31-40	6	13
5	41-50	3	8
6	51-60	4	8
7	61-70	3	9
8	71-80	2	2
9	81-90	2	1

Table 2. The distribution of uropathogens isolated from the urine specimen.

S/N	Name of bacteria	No. of isolates
1	*Escherichia coli*	39
2	*Klibsiella* spp.	15
3	*Protues mirabilis*	2
4	*Pseudomonas* spp.	2
5	*Enterobacter cloacae*	1
6	*Staph. aureus*	10
7	*Staphylococcus aureus* (MRSA)	1
8	*Enterococci* (one case of Group D)	3
8	*Staphylococcus saprophyticus*	1
9	*Staphylococcus epidermidis*	2
10	*Streptococcus agalactie*	2
11	*Candida* spp.	4
12	*Yeast*	1

Antibiotic sensitivity test

The antibiotic sensitivity test was performed using disc diffusion technique. In this procedure organisms isolated were inoculated in screw capped tube containing 5 ml normal saline (0.85%) with the help of disposable wire loop. The suspension of test organism was streaked over the surface of Muller Hinton agar plates using a sterile disposable cotton swab. Commercially available antibiotics discs were placed on plates firmly by means of sterile forceps aseptically and plates were incubated for 24 h at 35-37°C. Afterwards diameters of zone of inhibition were measured in mm. The antibiotics used and their zones of sensitivity was determined for further assessment.

Statistical analysis

Statistical tests (Z-test and Chi square test) were used to analyze the data by using statistical package SPSS 16.0 version. The Z-test was used to analyze the relationship between incidence of disease and gender while Chi square test was used to analyze the relation between disease and age.

RESULTS AND DISCUSSION

A total 115 patients of UTI of either sex (both male and female) with the respective ratio of 34:81 between age group of 1-90 years were studied (Table 1). A total of 83 (74.10%), specimen were analyzed to observe the antibiotic susceptibility having significant growth of uropathogens. the bacterial strains were either Gram positive or Gram negative pathogens, 04 were fungi indentified as *Candida* spp. (Table 2). One specimen showed yeast and two samples yielded of mixed bacterial growth. The antibiotics sensitivity test was performed for bacterial isolates only.

The indicator in CLED agar is bromothymol blue and therefore lactose fermenting colonies were appeared yellow like that of *E. coli, E. faecalis and S. aureus. The K. pneumoniae* and *S. saprophyticus* were observed to show yellow to white colonies. The growth appearance of *P. aeruginosa* colonies on CLED was green colonies with rough periphery and that of the *Proteus* spp. were translucent blue grey in color.

On MacConkey agar, *E. coli*, *Enterobacter* and *Klebsiella* produce acid, thus were results in the appearance of red/pink colonies. Non-Lactose fermenting bacteria such as *Proteus species* use peptone, forming ammonia and were leads to the formation of

white/colorless colonies.

Colony morphology of *E. coli* on blood agar was slightly convex, grey and moist with hemolytic property of some strains while *K. pneumoniae* showed white grey and usually mucoid colonies *Proteus mirabilis* showed swarming over entire surface and the ripples on water on blood agar. The colonies of *Enterococcus* species were observed to appear as grey, convex, smooth, shiny, and slightly opaque colony while *P.aeruginosa* showed large, flat, spreading colonies with clear zones of heamolysis. *S. agalactiea* produced mucoid colonies with clear area of β-hemolysis. *S. aureus* was seen to produce yellow to cream and occasionally to white colonies with β-hemolysis for some strains.

In this study incidence of infection was much higher in the patient between 21-30 years of age as compared to other age groups (Table 1). The most common isolates were *E.coli* (46.98%), *K. pneumoniae* (18.07%), *S. aureus* (12.04%), *Candida* spp. (4.81%), *Enterococci* (3.61%), *P. mirabilis*, *P. aeruginosea, S. epidermidis, S. agalactiea* (2.43%), each while *E. cloacae*, methicilline resistant *Staphylococcus aureus* (MRSA), *S. saprophyticus* were (1.20%). Two types of mixed pathogens were also found among total screened patient (Tables 2). The present results support the previous findings indicating that *E. coli* is the principal etiological agent of UTI, accounting for 46.98% of the screened cases (Jha and Bapat, 2005; Ronald, 1999a, b; Ronald, 1999, 2002). Moreover, 95% of Gram negative bacilli are responsible for UTI. *E. coli* remained dominant causing 80% of UTI followed by *Streptococcus* or *Staphylococcus* and *Proteus* species showing close resemblance to our findings (Lau et al., 2004). In another study, it was repoted, *E. coli* existed followed by *Klebsiella species* (Olafsson et al., 2000). Similarly it has also been reported that *E. coli* followed by *S. saprophyticus* was the most common uropathogen in females.

Results interpretation for antibiotic sensitivity

After 24 h of incubation, the culture plates with antibiotics discs were examined for the presence of growth inhibition, which is indicated by a clear zone surrounding Standards each disc. The susceptibility of organisms was determined, using Clinical and Laboratory Institute (CLSI) recommendations and expressed the results in mm; accordingly, the results were recorded in each investigation as from Sensitive (S) to Resistant (R) respectively.

It was found that the leading Gram negative uropathogen *E. coli* showed highest sensitivity (56%) to amikacin and low susceptibility (5%) to ciprofloxacin. It has also been reported as previously that amikacin was the most effective antibiotic against *E. coli* while ciprofloxacin showed lowest sensitivity against this pathogen (Schaeffer et al., 2001). The results were further supported by another study where the susceptibility rate of *E. coli* to amikacin remained 93-100% while (Shigemura et al., 2005). The previous reports concluded that ciprofloxacin (80%) had maximum sensitivity for Gram negatives and erythromycin (72%) for Gram positive organism (Stamm and Norrby, 2001). The highest resistance recorded in the present study for *E. coli* was (51%) to nalidixic acid and the lowest one was (5%) to nitrofurantoin which showed close resemblance to the results of another study which showed that the resistance rates of nitrofurantoin (6%), nalidixic acid (14%) for *E. coli* (Steven, 1989).

The highest sensitivity of *K. pneumoniae* observed was 80% to cefapime and low susceptibility 13% to ciprofloxacin which were further supported by the previous findings (Svanborg and Godaly, 1997). The highest resistance recorded was 60% in case of gentamicin which also bears closeness to other findings that among Gram-negative isolates maximum resistance was seen to cefuroxime 94% followed by netilmycin 82.5% and gentamycin 81.5% (Svanborg and Godaly, 1997). The lowest resistance recorded in our study was 6% to meropenem and nitrofurantoin for *K. pneumoniae*. In case of *P. mirabilis,* the resistance and sensitivity resulted were 50% to all the used antibacterial agents. The susceptibility of *E. cloacae* toward norfloxacin, nalidixic acid, imipenem, ceftazidine, pipercillin was 100%. The same pathogen was 100% resistant to augmentin. *P. aeruginosa* were 100% sensitive to augmentin, cefapime, aztreonam, nalidixic acid and norfloxacin. The resistance of the organism was 100% towards ceftazidine and imipenem while 50% for ciprofloxacin and pipercillin.

During observing the susceptibility of Gram positive bacterial pathogens it was noted that *S. aureus* showed highest sensitivity (64%) to augmentin similar to another study (Reid and Sobel, 1987). The 64% sensitivity rate as measured for oxacillin also showed resemblance to our results stated that the resistance rate for *S. aureus* was 34.2% (Taher and Golestanpour, 2009). The lower antibiotic sensitivity observed was for ampicillin which reflected concordance with another study showing sensitivity of *S. aureus* to commonly used antibiotics such as nalidixic acid and ampicillin was low (35%) (Talan et al., 2000). While measuring the zone diameter it was found that methicillin, erythromycin and cefotaxime were lying in the resistivity zone for *S. aureus* with 45% rate which showed resemblance to the previously reported study (Tankhiwale et al., 2004). The lower resistance was found for nitrofurantoin and trimethoprim.

In case of *Enterococcus* spp., the pathogen showed sensitivity of 67% for erythromycin, nitrofurantoin and norfloxacin and resistance of 33% for the mentioned antibiotics. *S. epidermidis* resulted 100% sensitivity to all subjected antibiotics. *S. agalactie* was 100% resistant to erythromycin and vancomycin while 50% resistance was seen for ampicillin, cefotaxime, ofloxacin, augmentin and methicillin. The *S. sapropyticus* was found 100% sensitive to erythromycin, vancomycin, augmentin,

Table 3. Antimicrobial sensitivity rates (%) of the Gram negative bacteria.

*Antibiotic (%)	*E. coli* (30)	*K. pneumoniae* (15)	*P. mirabilisa* (2)	*P. aeruginos* (2)	*E. cloacae* (1)
AMC	38	60	50	100	0
MEM	43	33	50	-	-
FD	25	26	50	50	-
FEP	30	80	50	100	-
CXM	15	40	0	100	-
LEV	30	53	50	-	-
NOR	23	20	50	100	100
PA/PIP	25	53	0	50	100
ATM	15	-	-	100	-
CTX	23	46	50	50	-
CAZ	46	60	50	0	100
NA	23	60	50	100	100
AM/AP	10	0	0	50	-
G/CN	23	40	50	50	-
IPM	41	-	-	0	100
FOS	33	20	-	-	-
SXT	12	26	-	50	-
AK	56	46	50	50	-
CIP	5	13	-	0	-

*AMC, Augmentin; MEM, meropenem; FD, nitrofurantoin; FEP, cefapime; CXM, cefuroxime; LEVO, levofloxacin; NOR, norfloxacin; PIP, pipercillin; ATM, aztreonam; CTX, cefotaxime; CAZ, ceftazidine; NA, nalidixic acid; AM/ AP, ampicillin; G/GM/CN, gentamicin; IPM, imipenem; FOS, fosfomycin; SXT, trimethoprim; AK, amikacin; CIP, ciprofloxacin.

trimethoprim and imipenem and showed 100% resistance to cefotaxime, norfloxacin and ceftazidine (Tables 3 and 4).

Jha and Bapat found the amikacin, the most effective for *E. coli* while ciprofloxacin showed lowest sensitivity against the pathogen (Schaeffer et al., 2001). Iqbal et al. (1997) concluded that Gram negative organism has maximum sensitivity for ciprofloxacin (80%) and Gram positive for erthromycin (72%) (Stamm and Norrby, 2001). A similar result pattern was noted by Azra et al. (2007), with resistance among isolates as 33.3% for *Staphylococcus aureus* and 63.5% average resistance for *Enterococci* (Tortora et al., 2006).

Ehinmidu (2003) reported that *E. coli, S. aureus* and *P. aeruginosa* strains were highly sensitive to ciprofloxacin and gentamicin having closeness to our observations in the obtained data (Winn et al., 2006).

Gender based and age based disease prevalence

The calculated value for Z-test (– 0.0248) and P-value (0.98) which is non-significant at 5% level of significance. The result rejects the hypothesis so it was concluded that the incidence of disease in females was high in comparison to males.

The values obtained from calculations for male patients were Chi-Square (7.504) P-value (.483) degrees of Freedom (8) which mean that the disease incidence can occur in male patients irrespective of the ages.

The values of Chi square test for female patients were Chi-Square (13.88) P-value (.085) degrees of Freedom (8) which mean that the disease incidence increases with the increasing age.

Conclusion

The appropriate treatment for UTI has been a subject of recent research. After statistical analysis it was concluded that the incidence of disease is higher in females than males. The study found that *E. coli, Klebsiella* spp. and *S. aureus* are the more common isolates in female subjects and in case of male patients *E. coli* also is principal etiological agent of UTI. The occurrence of UTI is significantly related to age in female patients, that is, the disease incidence increases with increasing age and vice versa for male patients. Identification of the causative organisms and its susceptibility to antimicrobials is important, so that proper drug is chosen to treat the patient in early stages of UTI. It is therefore recommended that routine microbiological analysis and antibiotic sensitivity test of mid stream urine samples of patients be carried out before the treatment in the management of UTIs. Our results suggest that the following antibiotics, amikacin, cefapime, norfloxacin,

Table 4. Antimicrobial sensitivity rates (%) of the Gram positive uropathogens.

*Antibiotics (%)	*S. aureus* (11)	*Enterococcus* spp. (3)	*S. epidermidis* (2)	*S. agalactie* (2)	*S. saprophyticus* (1)
E	18	67	100	100	100
VA	54	33	-	100	100
NA	_	-	100	-	-
AK	64	-	-	-	0
FD	27	67	-	-	-
AM	9	-	-	50	-
OX	64	-	-	-	-
CIP	55	33	-	-	-
IPM	45	-	-	-	100
CTX	18	0	100	50	0
OFX	55	-	-	50	-
SXT	27	33	-	-	100
FEP	36	-	-	-	-
AMC	64	33	100	50	-
NOR	18	67	100	-	0
CAZ	27	-	100	-	0
CXM	18	-	-	-	-
AMP	18	33	-	50	-
G/CN	55	33	-	-	100

*E, Erythromycin; VA, Vancomycin; NA, Nalidixic acid; AK, Amikacin; FD, Nitrofurantoin; AM/AP, Ampicillin; OX, Oxacillin; CIP, Ciprofloxacin; IPM, Imipenem; CTX, Cefotaxime; OFX, Ofloxacin; SXT, Trimethoprim; FEP, Cefapime; AMC, Augmentin; NOR, Norfloxacin; CAZ, Ceftazidine; CXM, Cefuroxime; AMP, Methicillin; G/GM/CN, Gentamicin.

ciprofloxacin, nalidixic acid, imipenem, oxacillin, erythromycin, nitrofurantoin, vancomycin, augmentin and trimethoprim can be chosen in management of UTIs by the clinicians after having the culture sensitivity results. Over and above for prevention of UTIs implementation of strict infection control guidelines, effective hand washing and judicious use of antimicrobials is mandatory which goes a long way to cope up, with the emergence of drug resistance among uropathogens.

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