ANTIMICROBIAL RESISTANCE OF UROPATHOGENS IN BASRAH

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ABSTRACT

***Background*: The high incidence of multi-resistant uropathogens is of great epidemiological significance because the etiological agents of urinary tract infection are quite capable of spreading through susceptible population.**

***Objective*: to study the extent of antimicrobial resistance of uropathogens in Basrah.**

***Patients & Methods*: A cross-sectional study involving 789 patients, 610 patients attending outpatient clinics in three hospitals in Basrah city and 179 admitted patients in Al-Sader Teaching Hospital, was carried out. Patients included in the study were those with symptoms suggestive of urinary tract infection and were not on antibiotics for at least one week. The study was conducted during the period between January 2003 and March 2004. For each patient a general urine examination and urine culture were done. Identification of the isolated bacteria was performed according to a standard method and antimicrobial susceptibility test was performed using the diffusion disk method.**

***Results*: Out of 610 outpatients included in the study, 443(72.6%) had positive culture, 128(61%) of males and 315 (78.8%) of females. *E.coli* was the commonest organism, isolated from 205 urine samples representing 43.7% of the total isolates, followed by other gram negative bacteria: *Klebsiella sp., Proteus sp., and Pseudomonas aeruginosa*. Gram positive cocci represented 7.7% & 3.6%.for CoPS and CoNS respectively. On the other hand, *Klebsiella sp* were the most commonly isolated bacterial uropathogens from inpatients, they represented 47.7% of the total isolates. Sensitivity rates to all chemotherapeutic agents among uropathogens isolated from hospital acquired urinary tract infections (the inpatient group) were lower than that of sensitivity rates of uropathogens isolated from the community acquired urinary tract infection. The overall sensitivity rates of isolates recovered from patients with hospital acquired urinary tract infection for norfloxacin, and ciprofloxacin were 59.3%, and 39.5%, while the sensitivity rates of the isolates reported from community acquired urinary tract infection for the same agents were 83.6%, and 39.5% respectively.**

***Conclusions*: Both hospital and community acquired uropathogens showed resistance to all classes of antimicrobial agents.**

INTRODUCTION

Most urinary tract infections are caused by facultative anaerobes that are able to grow under either anaerobic or aerobic conditions and usually originate in the bowel flora.[1] Pathogens associated with uncomplicated UTI are *E.coli* identified in about 75-90% of infections,[2] S*taphylococcus saprophyticus* (5-15%). *Klebsiella, Proteus, Enterococcus* and *Pseudomonas aeruginosa* are seen in smaller percentages.[3,4] There are an estimated 150 million UTI per annum worldwide.[5] UTI is the most common bacterial infection in women and accounts for significant morbidity and health cost.[5] In the USA, acute UTI encountered in adult women, resulting in as many as 8 millions office visits per year.[6] In United Kingdom, over 5 million prescriptions for antibiotics are written by general practitioners for UTIs annually.[7] There is increasing prevalence of antimicrobial resistance among uropathogens causing acute uncomplicated cystitis in young women.[8] Changing resistance pattern observed with common urinary pathogens has altered the empirical approach to antibiotics selection for UTI.[9] Appropriate antibiotic therapy is important because of the high incidence of UTI in the general population, the potential for complications, especially in high-risk subgroups, and the associated cost of treatment.[9] The high incidence of multi-resistant organisms is of great epidemiological significance because the etiological agents of urinary tract infection are quite capable of spreading through susceptible population.[10] Concurrent resistance to antimicrobials of

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different structural classes has risen in bacterial species and may complicate the therapeutic management of infections including those of urinary tract.[11] Routine antimicrobial resistance monitoring is therefore an essential part of any UTI control program that advocates empiric antimicrobial therapy.[12] The present study was carried out to study the extent of antimicrobial resistance of uropathogens in Basrah.

MATERIALS AND METHODS

A cross-sectional study involving 789 patients, 610 patients attending outpatient clinics in three hospitals in Basrah city, (namely Al-Sader Teaching Hospital, Basrah General Hospital, and Basrah Maternity and Children Hospital), and 179 admitted patients in Al-Sader Teaching Hospital, was carried out. Patients included in the study were those with symptoms suggestive of urinary tract infection and were not on antibiotics for at least one week. The study was conducted during the period between January 2003 and March 2004. Midstream urine samples were collected from each patient in a sterile universal container, brought to the laboratory and examined within one hour. General urine examination was carried out for each sample to screen for microscopic bacteriuria. Specimens which yielded 10^5/ml (CFU) or more were considered as having significant bacteriuria. [13] Urine cultures were done by spreading 0.1 ml of each sample on blood and MacConkey agars and incubated for 24-48 hours at 37°C. Identification of the isolated bacteria was performed according to a standard method. Antimicrobial susceptibility test was performed using the diffusion disk method.[14] The antimicrobial agents used in this study, were **β**-lactam, TMP-SMX, nitrofurantoin, gentamicin, and quinolones, because all of these agents achieve high urinary concentration.[15] Statistical analysis was done by using a computerized SPSS program, version 11.

RESULTS

Out of 610 outpatients included in the study (210 males and 400 females), 443(72.6%) had positive culture, 128 (61%) of males and 315 (78.8%) of females. *E. coli* was the commonest organism which was isolated from 205 urine samples representing 43.7% of the total isolates followed by other Gram negative bacteria. *Klebsiella sp., Proteus sp., and Pseudomonas aeruginosa* represented 25.4%, 11.3%, and 8.3% of the total isolates respectively. Gram positive cocci represented 7.7% & 3.6% for CoPS and CoNS respectively. (Table-1). On the other hand, *Klebsiella sp.* were the most commonly isolated bacterial uropathogens from inpatients, they represented 47.7% of the total isolates, while other bacterial uropathogens were present at various percentages as follows: E.coli (16.3%), Proteus *sp*., and *Pseudomonas sp.*(9.3%). Gram positive cocci: *Staphylococcus aureus* and CoNS represented 12.8% and 4.7% of the isolates respectively. (Table-1).

Table 1. Distribution of isolated urinary pathogens for outpatients, (Community Acquired UTI), and for inpatients (Hospital Acquired UTI)

Organisms	CA-UTI Frequency (%)	HA-UTI Frequency (%)
E .coli	205 (43.7)	14 (16.3)
Klebsiella sp.	119(25.4)	41 (47.7)
Proteus sp.	53 (11.3)	8 (9.3)
Pseudomonas aeruginosa.	39(8.3)	8 (9.3)
CoPS	36 (7.7)	11 (12.8)
CoNS	17 (3.6)	4 (4.7)
Total positive culture	469 (100)	86 (100)

Tables (2, 3, 4 & 5) demonstrate the overall resistance of different uropathogens to antimicrobial agents in community and hospital acquired UTI. In general, there are higher resistance rates to all antimicrobials in those cases with hospital acquired UTI than in cases with community acquired UTI for all uropathogens.

Table 2. Antimicrobial resistance of community versus hospital acquired UTI to Ampicillin, Amoxicillin, and Gentamicin

Organism	Ampicillin (%) Community / Hospital acquired UTI	Amoxicillin (%) Community / Hospital acquired UTI	Gentamicin (%) Community / Hospital acquired UTI
E. Coli	52.9/ 57.1	32.4 / 42.9	21.1/ 42.9
Klebsiella sp.	52.1 / 61	48.7 / 53.7	29.4/39
Proteus sp.	71.4 / 75	67.3 / 75	39.6/ 50
Pseudomonas sp.	56.4/87.5	64.1 / 75	35.9/50
CoPS	18.5 / 27.3	17.9 / 27.3	27.6 / 27.3
CoNS	22.2 / 25	22.2 / 25	11.1 / 25

Table 3. Antimicrobial resistance of community versus hospital acquired UTI to Nitrofurantoin and TMP-SMX

Organism	Nitrofurantoin (%) Community / Hospital acquired UTI	TMP-SMX (%) Community / Hospital acquired UTI
E. Coli	21.1 / 28.6	27.5 / 35.7
Klebsiella sp.	15.1 /19.5	36.1 / 39
Proteus sp.	56.3 / 62.5	39.6 / 50
Pseudomonas sp.	87.2 / 87.5	56.4 / 62.5
CoPS	16 / 27.3	24 / 27.3
CoNS	20 / 25	18.2 / 25

Table 4. Antimicrobial resistance of community versus hospital acquired UTI to quinolones.

Organism	Nalidixic acid (%) community/hospital acquired UTI	Ciprofloxacin (%) community/hospital acquired UTI	Norofloxacin (%) community / hospital acquired UTI
E. Coli	12.7/28.6	11.1/14.3	6.3/ 7.1
Klebsiella sp	13.4/ 29.3	10.1/ 17.1	8.4 /9.8
Proteus sp	33.3/37.5	12.5/25	4.2/ 12.5
Pseudomonas sp	56.4/62.5	12.8/25	5.1/ 12.5
CoPS	29.2/27.3	16/18.2	4 /9
CoNS	22.2/ 25	00/25	11.1/25

Table 5. Antimicrobial resistance of community versus hospital acquired UTI to cephalosporines.

Organism	Cephalexin (%) Community / Hospital acquired UTI	Cefotaxime (%) Community / Hospital acquired UTI	Ceftazidime (%) Community / Hospital acquired UTI	Cefixime (%) Community / Hospital acquired UTI
E. coli	25.5 / 35.7	21.6 / 28.6	11.2 / 14.4	23.9 /28.6
Klebsiella sp.	31.9 / 31.7	21 / 29.3	12.6 / 12.4	26.9 /29.3
Proteus sp.	33.3 /50	33.3 / 37.5	12.5 /12.5	27.1 /37.5
Pseudomonas sp.	56.4 / 50	35.9 / 37.5	10.3 / 12.5	33.3 /37.5
CoPS	19.2 / 27.3	28 / 27.3	8 / 9.1	25 /27.3
CoNS	18.2/ 25	22.2 / 25	11.1 / 00	22.2 /25

The overall sensitivity rates for hospital acquired uropathogens to different antimicrobial agents in comparison to that for community acquired uropathogens are shown in (Table-6). The highest sensitivity rates of community acquired uropathogens were for norfloxacin, ceftazidime & ciprofloxacin (83.6%, 78.7%, and 77.8% respectively), while the sensitivity rates of hospital acquired uropathogens for the same chemotherapeutic agents were 59.3%, 76.7% & 39.5% respectively. The lowest sensitivity rates were to ampicillin & amoxicillin, 18.3% & 21.2% respectively for community acquired uropathogens and 8.1% and 12.5% for hospital acquired uropathogens. In general the sensitivity rates were lower for hospital acquired uropathogens than the sensitivity rates of community acquired uropathogens.

Table 6. Sensitivity rates of community and hospital acquired urinary pathogens to different antimicrobial agents.

Antimicrobial agent	Sensitivity rate (%) Community acquired UTI	Sensitivity rate (%) Hospital acquired UTI
Norflaxacin	83.6	59.3
Ceftazidime	78.7	76.7
Ciprofloxacin	77.8	39.5
Gentamicin	54.5	25.6
Nalidixic Acid	50.5	33.7
Cefixime	50	15.5
Cefotaxime	38.5	27.7
TMP-SMX	37.2	26.7
Nitrofurantoin	35.1	32.6
Cephalexin	30.9	33.7
Amoxicillin	21.2	12.5
Ampicillin	18.3	8.1

DISCUSSION

Resistance to antibiotics has become a major international problem and there has been a worldwide effort to contain resistance by a number of interventions. The main strategy concentrates on surveillance of antimicrobial resistance and the feedback of surveillance to allow more rational prescribing.[16] Urine samples form a very significant part of the workload of microbiology laboratories and they can comprise up to 60% of specimens from the community, therefore, they can make an important contribution to surveillance to antibiotics resistance in the community.[16]

Antimicrobial resistance of community acquired uropathogens

An increase in antimicrobial resistance among pathogens that cause community acquired UTI was observed by several researchers.[3,17] In the present study, the antimicrobial resistance of *E. coli*, which was the commonest pathogen that caused community acquired UTI, was tested. The resistance rates to ampicillin, amoxicillin, and TMP-SMX, were found to be 52.9%, 32.4% & 27.5% respectively. While the resistance rates to gentamicin, and nitrofurantoin were equal at 21.1%. Similar rates were reported by several other studies.[3,18-20] Aminopenicillins are frequently used in treatment of a wide range of infectious processes including those in the UTI, so this frequent use has led to the resistance that was observed in the present study and that frequently seen in clinical isolates. [21] On the other hand, nitrofurantoin is a bactericidal in urine at therapeutic dose, and its multiple

mechanisms of action enable it to be potent against *E.coli* despite nearly 50 years of use. [22] However, the susceptibility level of *E.coli* may be influenced by, nitrofurantoin narrow spectrum of activity, limited, narrow tissue distribution and limited contact with bacteria outside the urinary tract.[23] *E. coli* resistance to the first generation quinolones was 12.7%, while resistance rates to second generation, ciprofloxacin and norfloxacin, were 11.7% and 6.3% respectively. Ciprofloxacin resistance rates in Europe ranged between 0% in Sweden and 14.7% in Spain.[19] Thus, it has been suggested that fluoroquinolones are logical choice for empirical therapy of uncomplicated UTI, but the wide spread use of fluoroquinlones for such common infections raises the possibility of accelerated development of resistance.[24] A gradual decrease in the susceptibility of *E.coli* to fluoroquinolones has been reported by the USA arm of the SENTRY surveillance program.[25] *Klebsiella sp*., the second commonest isolated uropathogens, showed high resistance to several antimicrobial agents (ampicillin, amoxicillin, TMP-SMX, and gentamicin). Similar results were reported in another study.[18] The resistance rate to ampicillin in Tikrit (1999) was found to be 98%.[20] *Klebsiella sp.* showed a lower resistance rates to third generation cephalosporines and to quinolones. These results are similar to those found in another study; with the exception that ciprofloxacin resistance rate was reported to be equal to 0%.[15] *Proteus species* resistance rates to different antimicrobial agents were found to be higher than those for other microorganisms. This may be due to their association with recurrent infection.[25] In the present study, *pseudomonas* species showed high resistance to the most common antimicrobial drugs (ampicillin, amoxicillin, TMP-SMX, nitrofurantoin, cephalexin, nalidixic acids and gentamicin). However, *Pseudomonas species* responded to third generation cephalosporines mainly to ceftazidime (resistance rate 10.3%). In Europe, ceftazidime and tobramycin resistance rates were 28.4% and 31.6% respectively. [26] Resistance of *Pseudomonas sp*. is an increasing clinical problem worldwide and is a recognized public health threat. There is limited number of antimicrobial agents with reliable activity against *pseudomonas sp*. [27]

Antimicrobial resistance of hospital acquired uropathogens

The hospital acquired uropathogens were resistant to all antibiotics. In this study *Klebsiella sp*. and *E.coli* were highly resistant to ampicillin, amoxicillin, gentamicin and TMP-SMZ. The resistance rates were higher than those found for community acquired UTI. In addition, *Klebsiella sp*. and *E.coli* showed a relatively high resistance rates to third generation cephalosporin and nitrofurantoin. The high resistance rates to gentamicin, third generation cephalosporin, and nitrofurantoin are in agreement with previous reports.[28,29] *Proteus sp*. and *Pseudomonas sp.* represent important uropathogens of nosocomial acquired infections, being widely distributed in hospital environment where they are difficult to eradicate. [30] In the present study, they showed high resistance rate to quinolones, aminoglycosides and third generation cephalosporines, thereby causing a major problem in the management of nosocomial UTI.

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