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Research Article

BACTERIAL RESISTANCE OF ANTIBIOTICS USED IN URINARY TRACT INFECTION

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ABSTRACT

The antibiotic resistance is a global problem and requires taking measures to combat this growing problem. One example is by quantifying prevalence of resistant pathogens. Our aim was to define the prevalence patterns of resistance to antibiotics among urinary tract infections by carrying out an appreciable survey in the medical laboratories department, Al-Thawra hospital, Sana'a city. The work was performed retrospectively as a cross-sectional descriptive study, gaining the required information from the patient's records in the medical laboratories. The results indicated that Escherichia coli was the most leading cause of urinary tract infections with 107 (52.2%) isolates followed by Pseudomonas aeruginosa with 39 (19%) isolates. Other species were Staphylococcus spp., Klebsiella spp., Proteus spp., and rarely Serratia and α-hemolytic Streptococcus spp.. The resistance pattern observed for these isolates, showed high resistance rates to the β-lactam antibiotic ampicillin and low rates to the aminoglycoside antibiotics gentamicin and amikacin. The resistance rates to trimethoprim-sulphamethoxazole, nalidixic acid and cefotaxim were also high. The uropathogens developed a moderate average resistance rates to ciprofloxacin and nitrofurantoin.

Keywords:

INTRODUCTION

Urinary tract infection (UTI) is a problem that is frequently encountered by health care providers. Over recent decades, the importance of UTI has been increasingly recognized, specifically, the role of UTI as an occult cause of febrile illness in infants[1].

It has been estimated that approximately 10% of humans are affected by UTI at sometimes during their lifetime[2] and 75% of patients treated by urologists are complaining of UTI [3]. The reported incidence in children during childhood is 1% in boys and 3% in girls[4].

Normally, urinary tract is sterile. The bacterial flora plays a part in either preventing or permitting uropathogens to colonize before ascent into the urinary tract [5]. The distal urethra has a sparse but complex and variable flora that is mainly of significance for the contamination it may introduce into urine collected for examination. The population consists of aerobic and anaerobic bacteria, [6, 7].

The infected urinary tract is a dynamic culture system in which bacteria multiply, the capacity of urine to support bacterial growth depends on its chemical composition, pH and osmolality [8], whereas some chemical constituents, such as glucose and amino acids, serve as bacterial nutrients [9, 10], others, such as urea and organic acids, act as growth inhibitors [11,12].

Escherichia coli is the commonest cause of all urinary tract infections [5]. Proteus species infections are particularly common in uncircumcised boys [13, 14]. Staphylococcus saprophyticus, is a primary uropathogen and is responsible for about 20% of urethritis and cystitis in sexually active except healthy women aged 16-25 years [15, 16] and sexually abused children [17].

The appropriate treatment of UTI has been relied on antibiotic use. The choice of antibiotic may be affected by local resistance patterns and other considerations such as the patient's age, sex and the infecting agent [18]. Due to rising antibiotic resistance among uropathogens, it is important to have local hospital based knowledge of the organisms causing UTI and their antibiotic sensitivity patterns [19, 20].

The poor information regarding antibiotic resistance in Yemen was the main cause that pushed us to carry out this study. We have chosen the field of urinary tract infections (UTIs) due to the high prevalence of these infections which have been reported to affect up to 150 million individuals annually worldwide [21], also the most common bacterial infection in women and account for significant morbidity and health care costs [22].

The study will give beneficial information that may help different specialties e.g. medical specialists and microbiologists; leading to change the manner of dealing with the bacteria of concern and also dealing with the antibiotics concerned in this study.

The aim of this study was to provide information regarding local resistance pattern of urinary pathogens to the commonly used antibiotics and to define the prevalence of antibiotic-resistant bacteria among symptomatic urinary tract infections.

MATERIALS AND METHODS

This retrospective study has been performed by the cross-sectional descriptive manner in order to measure the efficacy of eight antibiotics used to treat the urinary tract infection (UTI) among patients from all the age groups who showed symptomatic UTI.

This study was approved by the hospital's institutional review board and research ethics committee. The sample size was 205 and the duration of study was four months. The research team has gathered the required information from the medical laboratories department of Al-Thawra hospital in Sana'a city capital of Yemen

The collected samples, midstream urine, were gathered during the morning time from the patients, out- and in-patients, and tested for significant bacteriuria, then subjected to identification tests using the analytical profile index (API kits) to be followed by the antibiotic sensitivity test which was done using the disc diffusion method in Mullar Hington's agar. The results of the tests are stored in the computerized data base of the laboratory.

RESULTS

The sample size was 205 urinary tract infected patients, of which 116 (56.6%) males and 89 (43.4%) were females indicating that prevalence of the infected males is higher than females.

It is clear that in female the UTIs are more common among patient within 21 to 30 years of age, where as in males the UTIs are more prevalent among patient within 41 to 50 and above 60 year, as shown in Table 1.

E. coli was the most prevalent bacteria with a 107 (52.2%) isolates, 57 of which from males and 50 from females. Other bacteria were *Pseudomonas aeruginosa* (19%), *Klebsiella spp*. (10.7%), *Staphylococcus aureus* (6.8%), other *Staphylococcus spp*. (5.4%), other *Pseudomonas spp*. (1.5%), *Proteus spp*. (2.9%), *α-haemolytic streptococci spp*. (1%) and *Serratia spp*. (0.5%),as shown in the Table 2.

Table 1: distribution of UTI among various age groups.

Age group	Male number (%)	Female number (%)	Total number (%)
1day to 11 months	2 (1.7)	1 (1.1)	3 (1.5)
1 year to 10 years	9 (7.8)	7 (7.9)	16 (7.8)
11 years to 20 years	15 (12.9)	16 (18)	31 (15.1)
21 years to 30 years	18 (15.5)	28 (31.5)	46 (22.4)
31 years to 40 years	17 (14.7)	11 (12.4)	28 (13.7)
41 years to 50 years	20 (17.2)	7 (7.9)	27 (13.2)
51 years to 60 years	16 (13.8)	13 (14.6)	29 (14.1)
Above 60 years	19 (16.4)	6 (6.7)	25 (12.2)
Total	116 (100)	89 (100)	205 (100)

Table 2: Gender wise Distribution of Isolated Bacteria in Urine Samples

Bacteria	Male	Female	Total number (%)
Escherichia coli	57	50	107 (52.2)
Pseudomonas aeruginosa	32	7	39 (19)
Other Pseudomonas spp.	2	1	3 (1.5)
Staphylococcus aureus	6	8	14 (6.8)
Other staphylococci spp.	4	7	11 (5.4)
Klebsiella spp.	9	13	22 (10.7)
Proteus spp.	4	2	6 (2.9)
Serratia spp.	0	1	1 (0.5)
α-haemolytic streptococci spp.	2	0	2 (1)
Total	116 (56.6%)	89 (43.4%)	205 (100)

Among all the urinary pathogens mentioned in this study, the overall resistance was most common to ampicillin with 86%, trimthoprim-sulphamethoxazole with 73.8%, nalidixic acid with 71.9% and cefotaxime with 65.6%. In-addition, the percentage of resistance among the urinary bacteria was low (in relation to the other tested antibiotics concerned) to gentamicin with 15.3%, amikacin with 17.5%. Moderate percentages of resistance of 36.3% and 41.4% were noted in nitrofurantoin and ciprofloxacin respectively,as shown in table 3.

Table 3: Percentage sensitivity, intermediary and resistance among urinary pathogens.

Antibiotic	Sensitive%	Intermediate%	Resistant%
Amikacin (AK)	60.5	22	17.5
Gentamicin (GN)	64	20.6	15.3
Cefotaxim (CTX)	24.5	9.8	65.6
Ampicillin (AM)	9	5.1	86
Nitrofurantoin (F)	40.5	23.2	36.3
Ciprofloxacin(CIP)	51.4	7.2	41.4
Nalidixic acid (NA)	18.5	9.6	71.9
Trimethoprim-sulphamethoxazole(SXT)	16.9	9.2	73.8

E. coli was the first most cause of urinary tract infections with 107 (52%) cases. 15 (14%) of *E. coli* infected cases also had an associated yeast infection of candida species.

The resistance rate among *E. coli* to amikacin was 7.6% and gentamicin was 12.2%, constituting the lowest rate of resistance in relation to other antibiotics. 24.4% of *E. coli* isolates were resistant to nitrofurantoin. The resistance against the remaining drugs is generally elevated. *E. coli* shows the greatest resistance against ampicillin with 87.1% of *E. coli* isolates being resistant. The resistance patterns against nalidixic acid, cefotaxim and trimethoprim-sulphamethoxazole are closely related with 67.9%, 66.3% and 66.2%, respectively, of the isolates being resistant. Resistance to ciprofloxacin was reported in 44.7% of the *E. coli* isolates. Table 4 shows the resistance patterns of *E. coli* against the various antibacterial agents.

Table 4: Gender wise Distribution of Resistant E.Coli Isolates to Various Antibiotics

Gender	AK N(%)	GN N(%)	CTX N(%)	AM N(%)	F N(%)	CIP N(%)	NA N(%)	SXT N(%)
Male	5(62.5)	9(75)	35(61.4)	45(55.6)	14(63.6)	25(59.5)	29(54.7)	24(53.3)
Female	3(37.5)	3(25)	22(38.6)	36(44.4)	8(36.4)	17(40.5)	24(45.3)	21(46.7)
Total* N(%)	8 (7.6)	12(12.2)	57(66.3)	81(87.1)	22(24.4)	42(44.7)	53(67.9)	45(66.2)

AK: amikacin, GN: gentamicin, CTX: cefotaxime, AM: ampicillin, F: nitrofurantoin, CIP: ciprofloxacin, NA: nalidixic acid, SXT: trimethoprim-sulphamethoxazole; N: number of resistant isolates. *Total of resistant isolates.

Table 5: Gender wise distribution of resistant pseudomonas spp. Isolates to various antibiotics

Gender	AK N(%)	GN N(%)	CTX N(%)	AM N(%)	F N(%)	CIP N(%)	NA N(%)	SXT N(%)
Male	10(77)	5(55.5)	17(85)	28(82)	19(76)	12(86)	21(84)	21(77.7)
Female	3(23)	4(44.5)	4(15)	6(18)	6(24)	2(14)	4(16)	6(22.3)
Total* N(%)	13(31.7)	9(24.3)	21(63.6)	34(97.1)	25(75.8)	14(36.8)	25(86.2)	27(100)

AK: amikacin, GN: gentamicin, CTX: cefotaxime, AM: ampicillin, F: nitrofurantoin, CIP: ciprofloxacin, NA: nalidixic acid, SXT: trimethoprim-sulphamethoxazole; N: number of resistant isolates. *Total of resistant isolates.

Pseudomonas spp. was the second most cause of urinary tract infections with 42 (20.5% of the total) isolates, 39 (19%) of which are *P. aeruginosa* and 3 (1.5%) were other species. Ten of the *P. aeruginosa* isolates was associated with candidal infection. The resistance of *Pseudomonas spp*. to amikacin was within 31.7% all were *P. aeruginosa* while the other *Pseudomonas spp*., 3 cases only, were sensitive. 24.3% of the *Pseudomonas spp*. isolates were gentamicin resistant (also were *P. aeruginosa*, while the other spp. were sensitive). The resistance rate to nitrofurantoin was 75.8% (72.7% were *P. aeruginosa* and 3.1% other spp.). 97.1% of *Pseudomonas spp*. isolates were resistant to ampicillin (94.3% were *P. aeruginosa* and the remainder 2.8% were other spp.). Resistance to nalidixic acid was reported in 86.2% of the isolates (82.6% *P. aeruginosa* plus 3.6% other spp.). The resistance among

Pseudomonas spp. to cefotaxim was 63.6% (60.6% *P. aeruginosa* plus 3% others). Trimethoprim-sulphamethoxazole is completely ineffective, that is 100% of the *Pseudomonas spp*. are resistant. 33.3% of *Pseudomonas spp*. were resistant to ciprofloxacin (all are *P. aeruginosa* and no other resistant spp.). The resistance rates of *Pseudomonas species* among gender is indicated in table 5.

Staphylococcus spp. isolates were 25 (12.2%) of which 14 (6.8%) were *S. aureus* and 11 (5.4%) were other *staphylococci spp.* Two isolates of *S. aureus* were associated with *candida spp.*. 5.7% of *S. aureus* and 50% other spp. isolates were amikacin resistant and 14.3% and 9.1, respectively, were gentamicin resistant. Nitrofurantoin-resistant *S. aureus* and other *staphylococci spp.* were 10% and 28.6% respectively. 61.5% were ampicillin-resistant S. aureus, whereas 50% other spp. were ampicillin-resistant. The resistance rate of *S. aureus* and the other spp. to trimethoprim-sulphamethoxazole was 87.5% and 66.7% respectively. Nalidixic acid was resisted in 87.5% and 83.3% of *S. aureus* isolates and other spp. respectively. Resistance to ciprofloxacin and cefotaxim was reported in 38.5% and 72.7% of *S. aureus* respectively. The resistance rate among the other spp. to ciprofloxacin and cefotaxime were 37.5% and 55.6% respectively. Table 6 shows the resistance rates of pseudomonas species to various antibiotics.

Table 6: Frequency of resistant staphylococci isolates (including s. Aureus) to different antibiotics among gender

Gender	AK N(%)	GN N(%)	CTX N(%)	AM N(%)	F N(%)	CIP N(%)	NA N(%)	SXT N(%)
Male	5(50)	2(66.7)	6(46.2)	5(38.5)	1(33.3)	5(62.5)	5(41.7)	4(36.4)
Female	5(50)	1(33.3)	7(53.8)	8(61.5)	2(66.7)	3(37.5)	7(58.3)	7(63.6)
Total* N(%)	10(41.7)	3(12)	13(65)	13(56.5)	3(17.6)	8(38.1)	12(85.7)	11(78.6)

AK: amikacin, GN: gentamicin, CTX: cefotaxime, AM: ampicillin, F: nitrofurantoin, CIP: ciprofloxacin, NA: nalidixic acid, SXT: trimethoprim-sulphamethoxazole; N: number of resistant isolates. *the total of resistant isolates.

The *Klebsiella spp.* isolates were 22 (10.7%). 4 of *Klebsiella spp.* were associated with *candida spp.*. 4.8 % of *Klebsiella spp*. were resistant to amikacin and 9.5% were gentamicin resistant. 38.1% were nitrofurantoin resistant. 94.4% were ampicillin resistant. The resistance rate to trimethoprim-sulphamethoxazole was 56.3% and nalidixic acid was resisted in 52.6%. Resistance to ciprofloxacin 25% and Resistance to cefotaxim 64.7%. Table 7 shows the resistance rates of klebsiella species to various antibiotics. 6 (2.6%) were *Proteus spp*., 1 (0.5%) was *Serratia spp.* and 2 (1%) were *α-haemolytic streptococci spp*. The sample size of each was very small for statistical purposes.

Table 7: Frequency Of Resistant Klebsiella Spp to Different Antibiotics Among Gender

Gender	AK N(%)	GN N(%)	CTX N(%)	AM N(%)	F N(%)	CIP N(%)	NA N(%)	SXT N(%)
Male	1(100)	2(100)	7(63.6)	9(52.9)	6(75)	4(80)	7(87.5)	4(75)
Female	0(0)	0(0)	4(36.3)	8(47)	2(25)	1(20)	3(12.5)	5(25)
Total* N(%)	1(4.8)	2(9.5)	11(64.7)	17(94.4)	8(38.1)	5(25)	10(52.6)	9(56.3)

AK: amikacin, GN: gentamicin, CTX: cefotaxime, AM: ampicillin, F: nitrofurantoin, CIP: ciprofloxacin, NA: nalidixic acid, SXT: trimethoprim-sulphamethoxazole; N: number of resistant isolates. *the total of resistant isolates.

DISCUSSION

The aim of this study was to measure the resistance rate among uropathogens that cause symptomatic urinary tract infections (UTIs). The uropathogens identified were similar to those of many other studies in different countries [23], however results were different. The similarities and differences in the type and distribution of uropathogens may result from different environmental conditions and host factors, and practices such as healthcare and education programs, socioeconomic standards and hygiene practices in each country [24].

In contrast to most studies regarding urinary tract infections (UTIs), this study indicated a different sex distribution of patients showing predominance of males with UTI (56.6%), while females rate of UTI was lower (43.4%). This result could be contributed to the larger number of males patients visits to the laboratory department of the hospital in which the study was performed, also the social habits of most Yemeni males e.g. chewing Kat can be considered a contributing factor to the higher incidence of UTIs among males in this study.

In general, the resistance rates of bacteria isolated from males are higher than those of bacteria isolated from females to various antibiotics concerned in this study. However, the resistance rates of *Pseudomonas species* to amikacin, gentamicin and nitrofurantoin are higher among females than those of males. Also, resistance of *Staphylococcus species* is higher to trimethoprim-sluphamethoxazole and nitrofurantoin among females than males. Amikacin and gentamicin proved total efficacy against *Klebsiella species* without any resistant isolates.

The prevalence of *E. coli* was the highest with 52.2% among other uropathogens. Other pathogens are *Pseudomonas spp*. with 20.5% (19% *P. aeruginosa* and 1.5% other spp.), *Staphylococci spp*. with 12.2% (6.8% *S. aureus* and 5.4% other spp.), *Klebsiella spp* with 10.7%, *Proteus spp*. with 2.9%, *α-haemolytic streptococci spp*. with 1% and *Serratia spp*. with 0.5%. In Saint Camille Medical Center, Pakistan, a study indicated that *E. coli* was the leading agent responsible for the UTIs with 32.76%, followed by *S. aureus* 22.74% and *K. pneumonia* with 10.45% [1].

According to our study, a high level of resistance was seen to ampicillin in a rate of 86% (see table 3) where Pseudomonas and *Klebsiella species* form the highest rates of resistance to ampicillin with 97.1% and 94.4% respectively which is due to the production of β-lactamase. The resistance rates of *E. coli* and *Staphylococcus species* are 87.1% and 56.5% respectively. As indicated by many researchers [1], the resistance rate of *enterobacteria* to ampicillin was globally greater than 50%. Globally, the resistance rate of *E. coli* and *Klebsiella species* to ampicillin were 75.7% and 77.3% respectively, other studies indicated that the resistance rates were 62% and 90% respectively [25].

This study indicated that the overall resistance to Cefotaxim was 65.6% where the resistance rates of *E. coli*, *Pseudomonas species*, *Staphylococcus species* and *Klebsiella species* are closely related being 66.3%, 63.6%, 65% and 64.7% respectively. Other studies [24] reported a resistance rate of 53% also other studies indicated lower levels of resistance to cefotaxim.

Accordingly, the alarming resistance to such agents as cefotaxim requires periodic monitoring in order to take appropriate decisions when prescribing such antibiotics.

The lowest resistance levels were noted in this study to gentamicin 15.3% and amikacin 17.5% which make them the best choice among the other drugs studied in this work. Slightly elevated resistance rates to amikacin were reported in *Staphylococcus* and *Pseudomonas species* with 41.7% and 31.7% respectively, however, amikacin proved effective in *Klebsiella species* and *E. coli* with very low resistance rates of 4.8% and 7.6% respectively. Gentamicin is the most effective antibiotic in this study as the resistance rates among *E. coli*, *Pseudomonas*, *Staphylococcus* and *Klebsiella species* are 12.2%, 24.3%, 12% and 9.5% respectively.

Iranian study indicated that the most effective antimicrobial agents for treating UTIs are the aminoglycosides. [24].

The overall resistance rate to ciprofloxacin was 41.4%, this percentage is elevated when compared to other studies from Iran [24] that indicated resistance rate of less than 30%, other studies from Mexico indicated that the resistance to ciprofloxacin was 44% [26]; in our study, *E. coli* was the most resistant to ciprofloxacin with 44.7%, whereas Pseudomonas, Staphylococcus and Klebsiella species rates of resistance were 36.8%, 38.1% and 25% respectively.

The resistance also is elevated to nalidixic acid with an average rate of 71.9% which is much higher than that to ciprofloxacin, also as compared to study from Nigeria [27] which indicated a resistance rate of 23.9% among uropathogens to nalidixic acid. In our study, the resistance rates are very high among Pseudomonas and Staphylococcus species with 86.2% and 85.7% respectively, also high in *E. coli* and *Klebsiella* species with 67.9% and 52.6% respectively. Thus in our study the quinolone group antibiotics show effectiveness less than usual as compared to other studies. In the case of quinolones, the resistance patterns differ from region to another as exampled in ciprofloxacin discussion.

36.3% was the average resistance rate to nitrofurantoin in this study, other study from Iran indicated a rate of more than 50% resistant uropathogens. Mansour Amin et al. have reported a resistance level of about 63% to nitrofurnatoin. Our study indicated a very high rate of resistance to nitrofurantoin in *Pseudomonas species* with 75.8%, while the resistance rate in *Klebsiella species* was high with 38.1%, but in *E. coli* and *Staphylococcus species* there were slightly elevated rates of resistance to nitrofurantoin with 24.4% and 38.1% respectively.

The average resistance rate to trimethoprim-sulphamethoxazole was 73.8% so it is the second most resisted agent after ampicillin in this study. Trimethoprim-sulphamethoxazole is completely resisted by *Pseudomonas species* with a rate of 100%. *E. coli*, *Staphylococcus* and *Klebsiella species* showed also a very high rate of resistance with 66.2%, 78.6% and 56.3% respectively. The incidence of resistance to trimethoprim-sulphamthoxazole among uropathogens, particularly *E. coli*, varies considerably among different geographical locations [27].

CONCLUSION

Our study has presented useful information about the pattern of resistance among uropathogens. *E. coli* was, as expected, the leading cause of urinary tract infections (UTIs) both in general and among other Gram negative bacteria with 107 (52.2%) isolates, while *S. aureus* was the most prevalent among Gram positive bacteria with 14 (6.8%) isolates.

The study has indicated higher resistance rates to β-lactam antibiotics (ampicillin and cefotaxim) with ampicillin being the least effective agent for treating UTIs whereas the aminoglycoside antibiotics have been reported as the most effective agents with gentamicin being the least resisted agent.

Since the resistance rates of *E. coli*, *Pseudomonas*, *Staphylococcus* and *Klebsiella species* to ampicillin were very high with 87.1%, 97.1%, 56.5% and 94.4% respectively, this mean ineffectiveness of the empirical prescription of this agent to treat UTIs and hence it can only be prescribed after passing the antibiotic susceptibility test which will increase the cost of treatment.

The high rates of resistance to cefotaxim among *E. coli*, *Pseudomonas species*, *Staphylococcus species* and *Klebsiella species* with 66.3%, 63.6%, 65% and 64.7% respectively lead to conclude that this agent have been misused widely.

The aminoglycoside antibiotics (amikacin and gentamicin) proved high efficacy against uropathogens except the recognition that the resistance rates to amikacin were high in *Staphylococcus* and *Pseudomonas* species with 41.7% and 31.7% respectively, also a slightly elevated resistance rate of *Pseudomonas* species to gentamicin with 24.3%.

Although some studies have indicated an increasing resistance to ciprofloxacin by uropathogens[23], the resistance rates indicated in this study are very high which demands monitoring of ciprofloxacin prescription. The resistance rates to ciprofloxacin among *E. coli*, *Pseudomonas*, *Staphylococcus* and *Klebsiella species* were 44.7%, 36.8%, 38.1% and 25% respectively.

This study also indicated a high resistance rates to nalidixic acid. The rates of resistance in *E. coli*, *Pseudomonas*, *Staphylococcus* and *Klebsiella species* were 67.9%, 86.2%, 85.7% and 52.6% respectively.

The resistance rates to nitrofurantion varied considerably from slightly elevated to very high resistance rate, where *E. coli*, *Pseudomonas*, *Staphylococcus* and *Klebsiella species* had resistance rates of 24.4%, 75.8%, 38.1% and 38.1% respectively.

E. coli, *Pseudomonas*, *Staphylococcus* and *Klebsiella species* have very high resistance rates against trimethoprim-sulphamethoxazole with 66.2%, 100%, 78.6% and 56.3% respectively.

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