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Surveillance of urine cultures and evaluation gram negative uropathogens; five year data from Erbil

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Abstract

Objective: Urinary tract infections (UTIs) are most common infectious disease and a public health problem that imposes a large economic burden. Determining the distribution and resistance profiles of uropathogens in a region is important for planning empirical treatments, preventing antimicrobial drug resistance and establishing rational antibiotic use policies. The aim of this study is to gather surveillance data of urine cultures and determine the prevalence of uropathogens in urine samples of patients referred to outpatient clinics in Erbil region and to evaluate the antimicrobial susceptibility of the gram negative uropathogens.

Methods: All urine cultures result of patients referred to Erbil hospitals in the last 5 years (2015-2020) are retrospectively examined in this study. Microorganisms are identified by standard bacterial methods and their susceptibilities are assessed by VITEK 2 (bioMérieux, Marcy l'Etoile, France) automated system.

Results: The results of urine culture of 3380 suspected UTI cases are examined and out of 3097 positive cultures observed, a total of 1961 (63.3%) isolates are gram-negative and 1136 (36.7%) are gram-positive pathogens.

Conclusion: The most common urinary pathogen determined in this study is Escherichia coli. The highest resistances of gram-negative urinary pathogens are against the ampicillin, trimethoprim/sulfamethoxazole and ceftriaxone. It is thought that the data obtained from this study will be useful in the planning of empirical treatment of urinary tract infections and in the development of rational antibiotic use policies.

Keywords: Urine Culture, Urinary Tract Infections, Antimicrobial Resistance

INTRODUCTION

Urinary tract infections (UTIs) with a significant burden of economic are considered as common human's diseases of infectious and are a general health issue. UTIs, in the United States, are the most common urinary tract disease and are responsible for annual physician visits of more than 7 million and 15% of all antibiotics of community prescribed. Many European countries have similar incidence rates as well. (1) UTI-related health care costs are more than 3 billion $ per year globally (2). A systematic review by Beyer et al., reports the prevalence of UTIs in eight different countries to be between 17% and 82% (3). Gram-negative bacteria are the most common cause of UTI. The primary pathogens which lead to pyelonephritis and inflammation of uncomplicated bladder are *E. coli,* and other *Enterobacteriaceae* strains including *K. pneumoniae* and *P. mirabilis,* and gram-positive pathogens including *S. saprophyticus* and *E. faecalis* (4, 5). Urinary tract infections are common in women. A reason for this variation between the genders is due to anatomical differences such as a urethra of shorter and the fair urethra proximity to anus. Many other elements are involved, such as intercourse practices of sexual and utilizing spermicides that alter the natural flora of the vagina (6, 7).

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Several medications including fluoroquinolones, fosfomycin, trimethoprim-sulfamethoxazole, nitrofurantoin and beta-lactams are recommended in international recommendations for the treatment of pyelonephritis and tract infections of uncomplicated urinary tract infections (1, 5). Nevertheless, there is a worrying amount of resistance of antimicrobial in urinary pathogens because of the widespread and indiscriminate applying antibiotics. Broad-spectrum beta-lactamase-producing bacteria show resistance to several antibiotics regardless of carbapenem and are constantly enhancing within people (1, 8). Evaluation of pathogens and their sensitivity to different antibiotics has a high effect on the empirical treatment of patients with UTI, and if the appropriate antibiotic is selected by the physician, further costs and complications will be avoided. Health policies and rational antibiotic use protocols will be both more reliable and more applicable when created based on surveillance data.

The aim of this study is to provide surveillance data for the Erbil region and to evaluate the urine culture results according to gender and age groups and to reveal the contamination rates. Also, the prevalence of gram-negative pathogens and their antimicrobial susceptibilities in urine samples of patients referred to outpatient clinics in Erbil region.

METHODS

This cross-sectional-analytical retrospective study was performed to evaluate the results of urine culture of outpatients of Rzgary Teaching Hospital, Hawler Teaching Hospital, General Health Laboratory, and CMC Private Hospital which are all serving Erbil region during the years from 2015 to 2020. A total of 3380 samples were examined. Standard bacterial methods and biochemical tests together with VITEK 2 (bioMérieux, Marcy l'Etoile, France) automated identification system were used to identify uropathogens. VITEK 2 automated system was also used to evaluate antimicrobial susceptibilities of the causative bacteria according to Clinical & Laboratory Standards Institute: (CLSI Guidelines-M100). Outpatients over 18 years of age with positive urine culture reports were included in this study. Hospitalized patients and the patients who were younger then 18 years were excluded.

The results were evaluated based on the sex and age groups of 18-48 years, 46-60 years and more than 60 years. The antibiotic susceptibility panels including ampicillin, cefepime, aztreonam, cefixime, ceftriaxone, ertapenem, amoxicillin/clavulanate, piperacillin/tazobactam, amikacin, cefotaxime, imipenem, meropenem, ceftazidime, nitrofurantoin, levofloxacin, trimethoprim/sulfamethoxazole, ciprofloxacin and gentamicin were tested for the Gram-negative uropathogens.

As a limitation, since this study is retrospective, it was not possible to gather information such as previous or ongoing use of antibiotics which are not routinely questioned or recorded from outpatients.

Statistical Analyses

The data were analyzed using SPSS version 26.0 software (IBM Corp). The results of descriptive analysis were reported by tables and graphs. Chi-square test was used to examine the relationship between variables and a p value less then 0.005 is considered as significant.

RESULTS

Total number of 3380 urine cultures were evaluated retrospectively. Out 3380 cultures, 3097 (91.6%) were reported as positive. The contamination was determined in 95 (2.8%) of the cultures (Table 1). When evaluated according to age groups, there was not any significant difference in terms of "no growth", contamination or positive cultures ($p > 0.005$).

When all urine cultures were evaluated according to gender, 69.1% (n= 1045) of the urine cultures were requested from female outpatients where 30.9% (n= 2335) were from males. For the positive urine cultures, the ratios were similar and causative bacteria were more isolated from female patients. Moreover, significant difference was determined when positive urine cultures were evaluated according to age groups and sex. Urine culture positivity was higher in 18 to 45 years female age group compared to the male age group and in total (Table 2).

Table 1. Urine culture results according to age groups.

	18 to 45 years		46 to 60 years		>60 years		Total		
No growth	79	5.3%	56	5.8%	53	5.6%	188	5.6%	p > 0.005
Contamination	41	2.8%	22	2.4%	32	3.4%	95	2.8%	
Positive	1369	91.9%	877	91.8%	851	91%	3097	91.6%	
Total	1489	100%	955	100%	936	100%	3380	100%	

Among the positive urine cultures 1961 (63.3 %) of the isolates were gram-negative and 1136 (36.7%) were gram-positive pathogens. No significant difference was detected but gram-negative dominance was clearly observed between age groups and in total (Table 3).

The most common gram-negative pathogen identified was *E. coli*, which accounted for 70% of gram-negative isolates. *K. pneumoniae* (17%), *Proteus mirabilis* (3.9%) and *P. aeruginosa*

Table 2. Positive urine culture results according to age and sex groups.

	18-45 years		46-60 years		>60 years		Total		
Male	104	3.4%	326	10.5%	429	13.9 %	859	27.7%	p < 0.005*
Female	11265	40.8%	551	17.8%	422	13.6 %	2238	72.3%	
Total	1369	44.2%	877	28.3%	851	27.5%	3097	100%	

*For the 18 to 45 years group and when all age groups in total evaluated.

Table 3. Distribution of gram-negative and gram-positive pathogens according to age groups.

	18-45 years		46-60 years		>60 years		Total		
Gram-negative	867	28%	553	17.9%	541	17.5%	1961	63.3%	p > 0.005
Gram-positive	502	16.2%	324	10.5%	310	10%	1136	36.7%	
Total	1369	44.2%	877	28.3%	851	27.5%	3097	100%	

(3.4%) were the following most common pathogens, respectively (Table 4). Among gram-positive pathogens, coagulase negative *staphylococcus spp.* followed by *S. aureus* were most commonly isolated microorganisms.

Of the *Escherichia coli* isolates, 67.7% are resistant to ampicillin, 52% to TMP / SMX, 32.7% to ceftriaxone and 31.4% to cefixime. The lowest antibiotic resistance was reported to *Escherichia coli* for the antibiotics amikacin (0.2%), meropenem (0.3%), imipenem (0.4%) and ertapenem (0.4%). These four antibiotics also showed the highest sensitivity in other isolates. The pattern of resistance of antibiotics to *K. pneumoniae* was largely similar to that of *E. coli*. In *Enterobacter cloacae* complex isolate, the highest resistance was related to amoxicillin/clavulanate. Resistance to ertapenem and levofloxacin was reported in only three types of gram-negative urinary pathogens and the rest of the strains were quite sensitive. Only *S. marcescens* and *Salmonella* strains showed no resistance to Ciprofloxacin, and resistance to this antibiotic was observed in other strains (Table 5).

Table 4. Distribution of gram-negative uropathogens

Group	*Bacteria*	n	%
Fermentative (n=1868)	*E. coli*	1373	70.0
	K. pneumoniae	334	17.0
	P. mirabilis	77	3.9
	E. cloacae complex	27	1.4
	E. aerogenes	25	1.3
	K. oxytoca	12	0.6
	M. morganii	9	0.5
	S. marcescens	5	0.3
	Salmonella group	3	0.2
	Shigella group	3	0.2
Non-fermentative (n=93)	*P. aeruginosa*	67	3.4
	S. paucimobilis	4	0.2
	A. baumannii cplx	13	0.7
	A. haemolyticus	4	0.2
	A. lwoffii	5	0.3
Total		1961	100.0

Of the *E. coli* isolates, 38.6% were broad-spectrum beta-lactamase (ESBL) producing strains. However, the strains with the highest ESBL production were *Shigella group* (66.7%; 2 out of 3), *K. oxytoca* (41.7%; 5 out of 12) and *K. pneumonia*. (40.1%; 134 out of 334 cases). Overall, 35.5% (696 cases) of gram-negative isolates produced ESBL.

DISCUSSION

The problem of antimicrobial resistance in bacterial pathogens is described as a growing global crisis. The reported resistance to common pathogens in many parts of the world has reached a level where the experimental use of many of the strongest and most reliable antimicrobial agents available has been ineffective (9). The present study is unique because no research has been conducted with this large sample size in Erbil. The contamination rate is low as 2.8 % and there is no difference between age groups. This is compatible with literature. The urinary tract pathogens were determined higher in females in all age groups which is also as expected (4, 10). In general, the level of antimicrobial resistance among gram-negative uropathogens in Erbil is relatively high, which is a warning to prevent unnecessary use of antibiotics. Also in the present study, compared to others, the ratio of *E. coli* to other pathogens was higher. Therefore, the prevalence of *E. coli* is increasing compared to previous studies in Erbil.

Findings from previous studies have shown that resistance to antibiotics varies in different parts of the world. Developing countries such as India and Libya have reported very high resistance to conventional antibiotics (5). However, in the present study, antibiotic resistance was relatively high and it

Table 5: Antimicrobial resistance of gram-negative isolates.

Antibiotics	Gram negative uropathogens (percentage)														
	E coli	*K. pneumoniae*	*P. mirabilis*	*P. aeruginosa*	*S. paucimobilis*	*E. cloacae complex*	*A. baumannii*	*S. marcescens*	*Salmonella group*	*E. aerogenes*	*K. oxytoca*	*A. haemolyticus*	*A. lwoffii*	*M. morganii*	*Shigella group*
Ampicillin	67.7	74.9	59.7	29.9	25	0	0	0	0	0	58.3	0	0	55.6	33.3
Amoxicillin/Clavulanate	13.8	13.8	9.1	31.3	0	70.4	0	40	0	72	8.3	0	0	55.6	33.3
Amikacin	0.2	2.7	2.6	3	0	3.7	0	0	0	0	0	25	0	0	0
Aztreonam	5.9	6.9	1.3	0	0	3.7	0	0	0	8	16.7	0	0	0	33.3
Ceftazidime	25	33.2	3.9	10.4	0	48.1	30.8	0	0	44	16.7	0	0	11.1	66.7
Cefixime	31.4	31.4	7.8	31.3	25	48.1	0	20	0	52	0	0	0	11.1	0
Ciprofloxacin	26.5	9.3	10.4	6	25	3.7	30.8	0	0	4	16.7	25	20	11.1	33.3
Ceftriaxone	32.7	33.5	2.6	17.9	0	37	15.4	20	0	60	33.3	25	0	11.1	33.3
Cefotaxime	8.1	10.8	1.3	6	0	11.1	15.4	0	0	8	16.7	0	0	0	0
Ertapenem	0.4	0.9	1.3	0	0	0	0	0	0	0	0	0	0	0	0
Cefepime	4	4.5	2.6	3	0	3.7	7.7	0	0	8	0	0	0	0	33.3
Nitrofurantoin	2.1	7.8	62.3	25.4	0	0	7.7	40	33.3	12	0	0	0	33.3	0
Gentamicin	14.1	23.7	18.2	4.5	0	33.3	30.8	0	0	28	8.3	25	0	22.2	0
Imipenem	0.4	0.6	9.1	3	0	3.7	7.7	0	0	0	0	0	0	22.2	0
Levofloxacin	3.4	1.5	0	3	0	0	0	0	0	0	0	0	0	0	0
Meropenem	0.3	0.6	0	1.5	0	0	7.7	0	0	0	0	0	0	0	0
TMP/SXT	52	46.7	55.8	29.9	25	51.9	15.4	0	0	36	33.3	25	0	66.7	33.3
Piperacillin/tazobactam	4.9	3.3	0	9	0	7.4	30.8	0	0	24	16.7	25	0	0	33.3

*TMP/SXT: Trimethoprim/Sulfamethoxazole

seems that widespread and irrational use of antibiotics has caused this resistance. If available, planning of treatments depending on antimicrobial susceptibility testing results is a logical approach to prevent increased antimicrobial resistance. If antimicrobial susceptibility testing is not available, empirical treatment schemes should be designed with local data such as in this study to avoid the treatment failures with uneffective antibiotics.

In the present study, the most common uropathogen is *E. coli*, which accounted for 70% of gram-negative isolates, followed by *K. pneumonia* (17%), *Proteus mirabilis* (3.9%) and *P. aeruginosa* (3.4%). Previous studies have reported similar results. In the study of Ahmed et al. (2019), the most common uropathogens were *E. coli* (27%), *K. pneumoniae* (12.4%), *Proteus mirabilis* (4.5%) and *P. aeruginosa* (4.5%) (11). Aktaş and Denktaş (2017) identified *E. coli* as the most common strain (48%) among gram-negative pathogens, followed by *Klebsiella* (12). Abujnah et al. (2015) reported similar results in Libya. Osman (2019) Gupta et al. (2007) and Giwa et al. (2018) identified the most common gram-negative uropathogens as *E. coli*, *K. pneumoniae*, *P. mirabilis* and *P. aeruginosa* (13-16). The present study evaluated a larger sample than others, which increases the validity of the results.

In the present study, imipenem, meropenem, ertapenem and amikacin were the most effective antibiotics against gram-negative uropathogens (especially *Escherichia coli*). In the study of Aktaş and Denktaş (2020), *E. coli* strains showed the lowest resistance to these four antibiotics (12). A study by Ali et al. (2017) in Erbil showed the lowest resistance of *Escherichia coli* to imipenem (1.25%), meropenem and amikacin (1.9%) and Ertapenem (3.8%). These findings were consistent with our results. On the other hand, in the present study, *E. coli* strains showed the highest resistance to Ampicillin (67.7%), TMP / SXT (52%), Ceftriaxone (32.7%) and Cefixime (31.4%). Consistent with these findings, Edlin et al. Showed that *E. coli* strains in UTI patients were most resistant to ampicillin and trimethoprim / sulfamethoxazole (18). A study by Abujnah et al. (2015) in Libya showed that the resistance to ampicillin in *Escherichia coli* and *Klebsiella* species was 69.2% and 100%, respectively (16). Similarly, the study of Osman (2019) and Mohammed et al. (2016) reported the highest antimicrobial resistance to ampicillin (15,16,19) Gupta et al. (2007) reported resistance of co-trimoxazole, ampicillin and ciprofloxacin to the three uropathogens of *E. coli*, *K. pneumoniae* and *Pseudomonas* between 90% to 96%, 92% to 98% and 55% to 65%, respectively (14).

ESBL-producing bacteria are resistant to many common antibiotics, and the increasing prevalence of these bacteria is an indicator of increased antimicrobial resistance. In the present study, 38.6% of *E. coli* strains were ESBL positive. Aktaş and Denktaş (2020) reported 27.8% of *E. coli* samples as extended-spectrum beta-lactamase-producing strains (12). Given the novelty of the above study, it can be concluded that the prevalence of EBSL-producing strains of *E. coli* in Erbil, Iraq is higher than in Turkey. It appears to be because of the unscrupulous use of antibiotics in Erbil. According to previous studies, the treatment of ESBL-producing *E. coli*, which is commonly observed in community-acquired UTIs, is a challenge (20). In the study of Giwa et al. (2018), ESBL-producing strains generally accounted for 34.3% of cases (13). These findings were consistent with the results of present study with a 35.5% prevalence of ESBL-positive bacteria.

CONCLUSION

The most common gram-negative urinary pathogen determined in this study was *E. coli*. The highest resistances of gram-negative urinary pathogens were against the antibiotic ampicillin, trimethoprim/sulfamethoxazole and ceftriaxone, and the lowest resistances were for amikacin, meropenem, ertapenem and imipenem. The results of this study also show that Gram-negative uropathogens show significant resistance to trimethoprim/Sulfamethoxazole and ciprofloxacin, which are uncomplicated first-line therapies for UTI, and are unlikely to be ineffective. One of the best options for antibiotic treatment is fluoroquinolones, that show significantly low resistance levels. The data presented in this study, which was collected over a long period of time and had a large sample size, can be useful for planning empirical treatment schemes and setting appropriate and rational antibiotic use policies.

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Conflict of Interest

The authors declare that they have no conflict of interests regarding content of this article..

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Ethical Declaration

Ethical permission was obtained from the Sakarya University, Medical Faculty Clinical Research Ethics Committee for this study with date 30/06/2021and number E-40035, and Helsinki Declaration rules were followed to conduct this study.

Authorship Contributions

Concept: MSS, TD, MA; Design: TD, MA; Supervising: TD, MA; Financing and equipment: MSS, TD; Data collection and entry: MSS, HSG; Analysis and interpretation: MSS, HSG, TD, MA; Literature search: MSS, HSG; Writing: MSS, HSG, TD; Critical review: TD, MA.

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