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Original Article

The antibiotic susceptibility patterns of uropathogens isolated in Qassim, Saudi Arabia

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Abstract

Introduction: Antimicrobial resistance is a global health problem. The present study was carried out to determine the prevalence and antibiotic resistance of uropathogens in the outpatient departments (OPDs) at the clinics of Qassim University, Saudi Arabia.

Methods: A cross-sectional study was conducted from January to December 2016. Nonrepetitive midstream urine samples (1273) were cultured on standard culture media. Identification and susceptibility testing of causative microorganisms was performed using the fully automated VITEK 2 Compact system.

Results: Out of the 1273 nonrepetitive urine samples, 418 (32.8%) exhibited significant growth of UTI-causing microbes, 377 (90.2%) of which were Gram-negative bacilli. The commonly isolated microorganisms were *Escherichia coli* (157, 37.6%), *Klebsiella pneumoniae* (70, 16.7%), *Proteus mirabilis* (17, 4.1%), *Pseudomonas aeruginosa* (24, 5.8%), *Enterobacter cloacae* (11, 2.6%), *Enterococcus faecalis* (12, 2.9%), and *Staphylococcus aureus* (14, 3.3%). Overall, drug resistance was observed in 91.3% (n=381/418) of the samples, with a majority (80%) exhibiting resistance to at least 2 drugs. Drug resistance was commonly observed against ampicillin (89.9%), oxacillin (75.6%), piperacillin (85.4%), clindamycin (56.1%), amoxicillin/clavulanic acid (74.5%) and trimethoprim/sulfamethoxazole (50.4%).

Conclusion: The uropathogens *E. coli, K. pneumoniae* and *P. aeruginosa* and multidrug resistance pose serious therapeutic threats in the setting of this study. A concerted and systematic effort is required to rapidly identify high-risk patients and to reduce the burden of antimicrobial resistance in this region.

Key words: antimicrobial resistance; multidrug resistance; uropathogens; *E. coli*; *Klebsiella*; *P. aeruginosa*.

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Introduction

Urinary tract infections (UTIs) are a global health problem. According to the National Ambulatory Medical Care Survey and National Hospital Ambulatory Medical Care Survey, UTIs have accounted for nearly 7 million outpatient department (OPD) visits and one million emergency department visits, resulting in 100,000 hospitalizations [1]. Nearly 50–60% of all women suffer from at least one episode of UTI in their lifetime [2]. If the predisposing factors that are responsible for the occurrence of UTIs are not diagnosed and treated in a timely manner, UTI episodes might reoccur [3].

UTIs are commonly caused by bacteria, mostly Gram-negative bacteria, such as *Escherichia coli, Proteus* species, *Pseudomonas aeruginosa, Acinetobacter* species and *Klebsiella* species. Among Gram-positive bacteria, *Staphylococcus aureus, Enterococcus* species, *Staphylococcus saprophyticus* and coagulase-negative staphylococci are common bacteria that are predicted to be responsible for UTIs [4,5].

UTIs are often treated with broad-spectrum antibiotics, and treatment is initiated empirically, without performing culture and sensitivity tests. The inappropriate and nonjudicious use of antibiotics has resulted in the development of antibiotic resistance in bacteria worldwide, leading to the emergence of multidrug-resistant (MDR) strains of bacterial pathogens [6]. According to the European Survey of Antibiotic Consumption, resistant strains are responsible for a high mortality rate of approximately 25,000 Europeans yearly, and a considerable part of this increased mortality is caused by complications associated with UTIs [7]. The pattern of microbial resistance and the use of antibiotics differ considerably among various countries [8]. The Infectious Diseases Society of America recommends that regional surveillance be conducted to monitor changes in susceptibility of uropathogens in specific regions [9].

This study was carried out to assess the prevalence of uropathogens at the OPDs of the clinics at Qassim University, Saudi Arabia, and to examine the antibiotic susceptibility patterns of these uropathogens to build a database for future reference. There is little published data on the frequency of uropathogens and antimicrobial resistance in Saudi Arabia. These data will also help authorities formulate antibiotic prescription policies and evaluate antibiotic formulation guidelines. Increased awareness and annual reporting of these findings will help prevent emergent strains from spreading within the community.

Methodology

Study design and setting

The study was conducted from January to December 2016 among OPD at Qassim University clinics, Saudi Arabia. The study received ethical approval from the regional research ethics committee of Qassim Province, Saudi Arabia. The results of all non-repetitive midstream urine samples (1273 samples) submitted for urine culture and sensitivity testing were reviewed. Identification and susceptibility determination of the causative microorganisms was performed using the fully automated VITEK 2 Compact system.

Measurements

Colony counting was performed for numerical estimation of the number of viable bacteria in a milliliter of uncentrifuged urine; this is a quantitative estimation method that enables the differentiation of true bacteriuria from urethral or vulval contamination, which may occur during the collection of midstream or "clean-catch" urine [10]. Multiplication of microbes in the urinary system is defined by the presence of 10^5 or more colony-forming units (CFU)/mL of urine, which is significant diagnostic of UTI. Significant UTI was defined as urine culture plates with $\geq 10^5$ CFU/mL of freshly voided urine. Based on the cut-off of 10^5 CFU/mL, a positive urine culture was identified as $\geq 10^5$ CFU/mL of one predominant organism from a clean-catch specimen [10,11].

Collection and processing of urine samples

Urine samples were collected using a sterile container and were processed immediately. In the medical laboratory, each urine sample was divided into two; the first half was immediately inoculated on standard culture media. A standard quantitative method using a 1-µL loop and a 10-µL loop was followed to inoculate urine samples on cysteine-lactose-electrolyte-deficient (CLED) agar, MacConkey agar and blood agar (Oxoid, Basingstoke, UK). The plates were incubated aerobically at 35-37°C for 24 hours, and colony counting was performed using the standard quantitative loop (1 µL and 10 µL) method as follows: platinum loops or plastic disposable calibrated loops were used; A platinum-rhodium or disposable plastic 0.001-mL loop was used for colony counts > 1,000 CFU/mL, and a 0.01-mL loop was used for colony counts between 100 and 1,000 CFU/mL. Every set of 100 colonies was counted as 100 × 1 µL (1/1000 mL), which is equal to 100,000 or 10^5 CFU/mL of urine, which indicates a significant UTI. Then, the results were classified as significant/non-significant growth or contaminated (discarded). The second half of the urine was centrifuged (1500×g for 5 minutes) for direct microscopic examination.

A portion of the urine specimens was used for dipstick testing with rapid response urinalysis reagent strips (Combi-Screen PLUS, Roche, Indianapolis, USA). The presence of nitrite and leukocyte esterase was considered a positive indicator of active infection; however, when the dipstick test for nitrite and leukocyte esterase was negative, UTI was confirmed by urine culture testing.

Bacterial identification and susceptibility testing

Bacterial identification and antimicrobial susceptibility patterns were determined using the fully automated VITEK-2 Compact system (bioMérieux, La Balme-les-Grottes, France). Prior to application of the VITEK system, clinically significant isolates were subcultured for purity, inoculated on specific plates (nutrient agar or blood agar), and incubated aerobically at 35-37°C in 5% CO_2. Isolated bacteria were differentiated according to colony morphology and Gram staining. After overnight incubation, the pure bacterial colonies were used to prepare a standardized saline inoculum for the appropriate VITEK identification (ID) card. The following specific IC cards were used for identification of bacteria: Gram-negative ID card, (GN reference 21 341); Gram-positive ID card: (GP reference 21 342).

The antimicrobial susceptibility tests (ASTs) and the minimum inhibitory concentrations (MICs) were determined by using specific sensitivity cards (AST cards). The susceptibility tests were interpreted according to the Clinical and Laboratory Standards Institute (CLSI) criteria using the VITEK 2 system according to the manufacturer's instructions (bioMérieux, La Balme-les-Grottes, France) and the advanced expert system (AES). The following ATCC

strains were used for quality control: *E. coli* ATCC 25922, *P. aeruginosa* ATCC 27853 and *S. aureus* ATCC 29213. The AST cards included the Gram-negative sensitivity card (AST-N291 Reference 415 062) and Gram-positive sensitivity card (GP/AST-580 Reference 22 233). All methods, techniques, and processing steps were performed as described by the manufacturer. The VITEK 2 ID and AST cards were logged and loaded into the VITEK 2 Compact system. The VITEK 2 Compact system automatically reported and printed the results via VITEK 2 Systems software (version 06.01).

Isolated Gram-negative uropathogens were tested against different AST-N panels, including ampicillin, amoxicillin/clavulanic acid, piperacillin, piperacillin/tazobactam, cefalotin, cefuroxime, cefuroxime axetil, cefoxitin, cefpodoxime, cefotaxime, ceftazidime, cefepime, meropenem, amikacin, gentamicin, tobramycin, ciprofloxacin, norfloxacin, nitrofurantoin and trimethoprim/sulfamethoxazole.

Gram-positive uropathogens were tested against AST-Ps, including benzyl penicillin, oxacillin, a cefalotin screen, gentamicin, tobramycin, levofloxacin, moxifloxacin, erythromycin, clindamycin, inducible clindamycin resistance, linezolid, teicoplanin, vancomycin, tetracycline, tigecycline, fosfomycin, nitrofurantoin, fusidic acid, rifampicin, mupirocin, and trimethoprim/sulfamethoxazole P.

Data collection and statistical analysis

The ages and genders of the subjects who provided specimens were recorded, and the data were then exported into a spreadsheet for statistical analyses. We used descriptive statistical methods to analyze the data. The prevalence of antimicrobial resistance was estimated as the proportion of positive results over the entire study sample. MDR strains were defined as strains resistant to at least two antimicrobial agents.

Results

During the period from January to December 2016, a total of 1273 nonrepetitive urine samples for culture and sensitivity tests were received by the microbiology laboratory. Of these urine samples, 418 (32.8%) exhibited significant growth. A vast majority of these samples were from females (345, 82.5%). The mean (SD) age was 36.5 (12.2) years.

Urinary pathogens

The 418 total bacterial uropathogens isolated from the urine samples comprised 377 (90.2%) Gram-negative and 41 (9.8%) Gram-positive strains. The most common urinary pathogens isolated were *E. coli* (157, 37.6%), *followed by Klebsiella pneumoniae* (70, 16.7%), *P. aeruginosa* (24, 5.7%), *Morganella morganii* (18, 4.3%), and *Proteus mirabilis* (17, 4.1%) (Table 1).

Table 1. Frequency distribution of uropathogens isolated in Qassim, Saudi Arabia.

Genus	Species	Frequency	Percent
Gram-negative bacteria isolates = 377 (90.2%)			
Escherichia	*E. coli*	157	37.6
Klebsiella	*K. pneumonia*	70	16.7
	K. oxytoca	6	1.4
Proteus	*P. mirabilis*	17	4.1
	P. vulgaris	5	1.2
Pseudomonas	*P. aeruginosa*	24	5.7
	P. luteola	9	2.2
Enterobacter	*E. cloacae*	11	2.6
	E. aerogenes	7	1.7
Morganella	*M. morganii*	18	4.3
Pantoea	*P. agglomerans*	9	2.2
Citrobacter	*C. freundii*	11	2.6
Acinetobacter	*A. baumannii*	17	4.1
	A. lwoffii	7	1.7
Serratia	*S. marcescens*	5	1.2
	S. fonticola	4	1
Gram-positive bacterial isolates = 41 (9.8%)			
Enterococcus	*E. faecalis*	12	2.9
	E. faecium	6	1.4
Staphylococcus	*S. aureus*	14	3.3
	S. saprophyticus	9	2.2
Total	**20**	**418**	**100**

Table 2. Percentage of common gram negative urinary pathogens resistant to antimicrobial agents.

Antimicrobial agents	***E.coli***	***Klebsiella pneumonia***	***Klebsiella oxytoca***	***Proteus mirabilis***	***Proteus vulgaris***	***Pseudomonas aeruginosa***	***Pseudomonas luteola***	***Enterobacter cloacae***	***Enterobacter aerogenes***	***Morganella morganii***	***Pantoea agglomerans***	***Citrobacter freundii***	***Acinetobacter baumannii***	***Acinetobacter lwoffii***	***Serratia marcescens***	***Serratia fonticola***
Ampicillin	93	97.1	100	70.6	60	100	100	100	85.7	94.4	33.3	90.9	82.4	42.9	60	100
Amoxicillin/ clavulanic acid	72	77.1	66.7	64.7	60	95.8	100	81.8	85.7	94.4	33.3	81.8	64.7	42.9	60	75
Piperacillin	93	97.1	100	64.7	60	100	100	63.6	57.1	88.9	11.1	72.7	70.6	42.9	20	75
Piperacillin/ tazobactam	55.4	57.1	50	64.7	60	100	100	36.4	14.3	88.9	11.1	54.5	58.8	42.9	0	100
Cefalotin	77.7	52.9	66.7	70.6	60	95.8	100	100	85.7	94.4	33.3	81.8	64.7	71.4	60	75
Cefuroxime	86	45.7	50	70.6	60	95.8	100	54.5	14.3	100	77.8	72.7	64.7	42.9	20	75
Cefuroxime axetil	54.8	52.9	50	70.6	60	95.8	100	72.7	57.1	100	77.8	72.7	64.7	57.1	60	75
Cefoxitin	15.9	17.1	33.3	47.1	60	95.8	88.9	54.5	71.4	38.9	66.7	54.5	64.7	57.1	60	0
Cefpodoxime	27.4	42.9	50	58.8	60	95.8	100	72.7	57.1	100	77.8	72.7	58.8	57.1	60	75
Cefotaxime	26.1	42.9	50	64.7	60	95.8	100	36.4	14.3	94.4	22.2	63.6	52.9	28.6	60	75
Ceftazidime	31.2	42.9	50	64.7	60	100	100	36.4	14.3	100	66.7	63.6	58.8	57.1	20	75
Cefepime	31.2	40	50	64.7	60	95.8	100	36.4	14.3	94.4	11.1	45.5	23.5	42.9	20	75
Meropenem	6.4	10	33.3	17.6	100	33.3	33.3	100	0	0	0	0	0	0	20	0
Amikacin	10.2	14.3	33.3	29.4	100	20.8	22.2	18.2	14.3	5.6	0	27.3	5.9	28.6	0	50
Gentamicin	14	38.6	33.3	52.9	100	41.7	33.3	18.2	14.3	66.7	66.7	45.5	23.5	28.6	40	75
Tobramycin	48.4	44.3	50	52.9	100	37.5	44.4	18.2	14.3	16.7	66.7	63.6	23.5	42.9	20	75
Ciprofloxacin	56.1	34.3	50	58.8	20	66.7	55.6	27.3	14.3	33.3	22.2	72.7	47.1	42.9	0	0
Norfloxacin	56.1	35.7	50	47.1	20	66.7	55.6	27.3	14.3	33.3	22.2	72.7	47.1	42.9	20	0
Nitrofurantoin	14.6	82.9	83.3	94.1	100	95.8	88.9	63.6	71.4	100	44.4	54.5	64.7	42.9	60	100
Trimethoprim/ sulfamethoxazole	49	47.1	33.3	58.8	20	100	88.9	63.6	42.9	33.3	44.4	36.4	41.2	42.9	20	0
Total no. of isolates	157	70	6	17	5	24	9	11	7	18	9	11	17	7	5	4

The antimicrobial resistance patterns of Gram-negative bacteria to various antibiotics are shown in Table 2. For example, the common urinary pathogens *E. coli, K. pneumoniae*, and *P. aeruginosa* exhibited very high frequencies of resistance to amoxicillin/clavulanic acid, piperacillin, and ampicillin. In comparison, low resistance rates were observed against amikacin and meropenem. *E. coli* exhibited a relatively low rate of resistance to nitrofurantoin (14.6%) compared with *K. pneumoniae* (82.9%), *P. aeruginosa* (95.8), and *P. mirabilis* (94.1%). *E. coli* was almost completely resistant to ampicillin, amoxicillin/clavulanic acid, piperacillin, cefalotin, and cefuroxime and moderately resistant to piperacillin/tazobactam, cefuroxime axetil, ciprofloxacin, norfloxacin, and trimethoprim/sulfamethoxazole. High rates (> 70%) of ampicillin, amoxicillin/clavulanic acid, piperacillin, and nitrofurantoin resistance in *K. pneumoniae* were also observed. Gram-positive isolates, as shown in Table 3, demonstrated 100% resistance to benzyl penicillin and relatively low rates of resistance to linezolid, teicoplanin, vancomycin, and tigecycline.

Multiple-drug resistance

Both Gram-negative and Gram-positive bacteria were affected by the emergence of and increase in antimicrobial resistance. Multiple-drug resistance was high among the isolated urinary pathogens. In particular, *Pseudomonas* spp. were susceptible to amikacin and meropenem and exhibited resistance (88.9 to 100%) to at least 13 antimicrobial agents. *E. coli* and *K. pneumoniae* exhibited > 60% resistance rates to at least four of 20 antimicrobial agents (Table 2). *Enterococcus faecalis* was 100% resistant to 5 antimicrobial agents (Table 3).

Discussion

UTIs are among f the most common bacterial infections caused by a wide spectrum of Gram-negative and Gram-positive bacteria [3]. In our study, the proportions of female patients with UTIs was higher than that of males. This result is consistent with the findings of Kattel et al. [12]. Various factors have been proposed to be responsible for the predisposition of women to UTIs [13].

The most prevalent uropathogens in the current study were *E. coli* and *K. pneumoniae.* This result is consistent with those of other studies from Saudi Arabia, which found that *E. coli*, *K. pneumoniae* and *E. faecalis* constituted 66, 11.4, and 5.4%, respectively, of the most prevalent uropathogens [14,15].

The prevalence of UTIs and the antibiotic resistance observed in this setting were higher than those observed in a previous study conducted in 1995 in the same area. For example, in our study, the prevalence of UTIs caused by urinary pathogens was found to be 37.6%. This value is slightly higher than that obtained in a

Table 3. Percentage of common Gram-positive urinary pathogens resistant to antimicrobial agents.

Antimicrobial agents	*Enterococcus faecalis*	*Enterococcus faecium*	*Staphylococcus aureus*	*Staphylococcus saprophyticus*
Benzyl penicillin	100	100	100	100
Oxacillin	100	100	78.6	22.2
Cefalotin screen	16.7	66.7	0	0
Gentamicin	100	83.3	7.1	0
Tobramycin	100	100	7.1	0
Levofloxacin	33.3	50	14.3	0
Moxifloxacin	25	50	0	0
Erythromycin	58.3	50	42.9	66.7
Clindamycin	75	83.3	57.1	11.1
Inducible clindamycin resistance	0	0	35.7	11.1
Linezolid	16.7	0	0	0
Teicoplanin	8.3	0	35.7	11.1
Vancomycin	8.3	0	35.7	11.1
Tigecycline	8.3	0	7.1	0
Fosfomycin	100	100	21.4	0
Nitrofurantoin	33.3	66.7	0	0
Fusidic acid	100	100	28.6	77.8
Rifampicin	100	100	35.7	11.1
Mupirocin	66.7	83.3	0	0
Trimethoprim/sulfamethoxazole	91.7	83.8	0	0
Total no. of isolates	12	6	14	9

study conducted by Ahmad S in 1995 in King Fahad Specialist Hospital in Buraydah, Qassim Province, Saudi Arabia, who observed a prevalence of 20.54% [16]. Furthermore, we found that the distribution of the common pathogens was slightly different from those observed in previous studies in the same area. The most commonly isolated pathogen was *E. coli* (50.11%), followed by *Klebsiella* spp. (28.33%) *Pseudomonas* spp. (7.84%) and *Proteus* spp. (4.91%). However, in our study, the most common pathogens were *E. coli* (37.6%), *K. pneumoniae* (16.7%), *E. cloacae* (2.6%), *P. mirabilis* (4.1%) and *P. aeruginosa* (5.7%). The prevalence of *E. coli* decreased and that of *Enterococcus* spp. increased. In this study, there was a significant discrepancy between UTIs caused by commonly isolated bacteria and those caused by relatively less commonly isolated bacteria at this location.

A striking finding from this study was the degree of drug resistance among key pathogens. We observed a very high rate of resistance (> 70%) among *E. coli* isolates to ampicillin, piperacillin, cefalotin, and amoxicillin/clavulanic acid. Among *K. pneumoniae* isolates, low resistance was observed against meropenem (10%), ciprofloxacin (10%), norfloxacin (35.7%), and cefotaxime (42.9%), but high resistance was observed against ampicillin, amoxicillin/clavulanic acid, piperacillin, and nitrofurantoin. *P. aeruginosa, E. cloacae and M. morganii* exhibited similar patterns of resistance to piperacillin, piperacillin/tazobactam, ceftazidime and trimethoprim/sulfamethoxazole, and the values were consistently greater than 75% [17]. These patterns were probably due to extensive use of third-generation cephalosporins and quinolone antibiotics by patients with UTIs. Therefore, these pathogens are increasingly being recognized as important causes of UTIs, and our findings confirm the significance of these species as leading causes of MDR infections in patients with UTIs. The uropathogenic bacterial etiology and susceptibility to antimicrobial agents are known to change over time and vary among countries [9,18,19]. Susceptibility to cotrimoxazole is an determinant of UTI treatment, as suggested by the European Urology Association (EUA) guidelines [20], which recommend cotrimoxazole as the first-line drug for empirical treatment of community-acquired UTIs when the local rates of resistance of uropathogens to trimethoprim/sulfamethoxazole are <10–20%. However, our study revealed an overall resistance of 50.4% and *E. coli*-specific resistance of 49.0% to this antibiotic. Similar results were obtained in a recent study of this nature [21] conducted in the Sultanate of Oman, which revealed an overall resistance of 47% and *E. coli*-specific resistance of 50% to this antibiotic. This finding is in contrast to reports from European countries of low resistance rates, ranging from 28% to 30% [22,23], and to those from African countries of high resistance rates, ranging from 88.3% to 98.6% [24,25].

On the other hand, the use of laboratory tests is necessary for reliable diagnosis and to provide specific information regarding the identities and antimicrobial susceptibility patterns of pathogens. Indeed, both laboratory and clinical diagnosis of laboratory test results must be based on the method of collection used.

As part of infection control, we implemented a program using the VITEK system to detect and report uropathogenic etiology and to limit the therapeutic failures that may inherently be caused by the use of conventional methods. The phenotyping techniques that were used to identify uropathogenic bacteria and to confirm the antimicrobial resistance data profiles were consistent with previously used molecular genotyping methods.

In contrast to other previously conducted studies, particularly in the same country, we used a fully automated machine. Use of the VITEK 2 system enabled the identification of a broad spectrum of bacteria and determination of the susceptibility of these bacteria to up to 20 different antimicrobial agents.

Our findings have important clinical implications for the treatment and management UTIs, particularly those caused by MDR uropathogens. First, clinicians should realize that there is a high possibility that patients with UTIs can be infected with common uropathogens as well as relatively less commonly isolated uropathogens and that multiple-drug resistance exists. Second, the high rate of multidrug resistance observed in this study is a serious concern for the management of UTIs and calls for a systematic approach to reduce antibiotic resistance rates or to minimize the use of broad-spectrum antimicrobial agents. Third, in the presence of multidrug resistance, the development of rapid diagnostic tests (point-of-care testing) for prompt targeted therapy is an important priority. There is also a need for implementation of a drug-monitoring system that optimizes drug administration and enables a personalized approach to proposed treatments.

We believe that UTIs represent an accessible target for the development of health education programs aimed at reducing the prevalence of diseases in communities and improving the quality of life for patients in low- and middle-income areas.

Conclusion

The uropathogens *E. coli, K. pneumoniae,* and *P. aeruginosa* and multidrug resistance pose serious therapeutic threats in the setting of this study. A concerted and systematic effort is required to rapidly identify high-risk patients and to reduce the burden of antimicrobial resistance in this region.

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