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Original Article

Antimicrobial susceptibility of microorganisms causing Urinary Tract Infections in Saudi Arabia

Bander Balkhi[1], Wael Mansy[1], Sultan Alghadeer[1], Abdulrahman Alnuaim[2], Abdullah Alshehri[3], Ali Somily[4]

[1] *Department of Clinical Pharmacy, College of Pharmacy, King Saud University, Riyadh, Saudi Arabia*
[2] *Johns Hopkins Aramco Healthcare Center, Dhahran, Saudi Arabia*
[3] *Prince Mohammad Bin Abdulaziz Hospital, Riyadh, Saudi Arabia*
[4] *Department of Pathology and Laboratory Medicine, College of Medicine, King Saud University and King Saud University Medical City, Riyadh, Saudi Arabia*

Abstract
Introduction: Urinary Tract Infections (UTIs) is one of the most common infections worldwide. UTIs remain a challenge to the healthcare system because of the emergence of antimicrobial resistance. The aim of this study is to report the most common UTI-causative organisms associated with the emergence of antimicrobial resistance in Saudi Arabia.
Methodology: a retrospective cross sectional study of 1918 positive urine culture samples of both gender collected over 9 months (May 2015 to February 2016) from a major tertiary hospital in Riyadh, Saudi Arabia.
Results: the median age of individuals involved in the study was 43 years, with males constituting 27.7% only of the population. Among cases deemed complicated (81.1%), common causes were diabetes, pregnancy, and immunocompromization, comprising 24.7%, 11.9%, and 10.8%, respectively. *Escherichia coli* (52%) was the most common uropathogen, followed by *Klebsiella pneumoniae* (15%), *Pseudomonas aeruginosa* (8%) *Streptococcus agalactiae* (Group B *streptococcus)* (7%), and *Enterococcus faecalis* (5%). Overall sensitivity studies showed the most highly resistant uropathogen was *Escherichia coli* (60%) followed by *Klebsiella pneumoniae* (16%), *Pseudomonas aeruginosa* (4%) *Enterococcus faecalis* (3%), and *Enterobacter cloacae* (2%). Concerning the first defense antibiotics prescribed for UTI, *E. coli* was most frequently resistant to Sulfamethoxazole/Trimethoprim (47%) followed by ciprofloxacin (34%). *K. pneumoniae* was most frequently resistant to Sulfamethoxazole/trimethoprim (35%) followed by cefuroxime (30%), while *P. aeruginosa* to ciprofloxacin (13%).
Conclusion: Because of a high level of antimicrobial resistance amongst uropathogens in Saudi Arabia, the development of regional and national UTI guidelines is recommended.

Key words: urinary tract infection; antimicrobial resistance; uropathogen, Saudi Arabia.

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Introduction

Urinary tract infections (UTI) are one of the most common bacterial infections in humans, both in the community and hospital settings [1]. Based on the location, UTIs are divided into three types; descending, ascending and complicated UTIs. Descending UTIs, also known as cystitis, are associated with polyuria, dysuria, and urgency. Ascending UTIs, also known as pyelonephritis, are associated with fever or flank pain in addition to urinary symptoms. Complicated UTIs are associated with comorbid conditions such as diabetes, pregnancy and manhood [2]. Worldwide, approximately 150 million people are diagnosed with UTIs, causing a heavy burden on the health financial system, with around 6 billion dollars in health care spending each year [3,4].

The most frequent causative microorganisms of UTI are mainly gram negative organisms such as *E. coli*, *K. pneumoniae*, *Acinetobacter baumannii* and *P. aeruginosa*. Furthermore, gram positive organisms such as *Staphylococcus saprophyticus*, Methicillin-resistant *Staphylococcus aureus* (MRSA) and *Enterococcus species* can also cause UTI [5].

Bacteriological investigations of UTIs are not complete without an antibiotic sensitivity test of the isolate. Microorganisms causing UTIs vary in their susceptibility to antimicrobials from place to place and time to time [6]. Knowledge of the local bacterial etiology and susceptibility patterns is required to trace any change that might have occurred in time so that updated recommendations for optimal empirical therapy of UTIs can be made [7]. The Infectious

Diseases Society of America (IDSA) published clinical practice guidelines on the treatment of women with acute uncomplicated cystitis and pyelonephritis [8]. Since then, antimicrobial resistance among uropathogens, and appreciation of the importance of the ecological adverse effects of antimicrobial therapy (collateral damage), has increased, newer agents and different durations of therapy have been studied, and clinical outcomes have increasingly been reported [2,9].

Antibiotic resistance among causative gram-negative bacilli is increasing and considered to be a challenge for clinicians because there are limited treatment options. Common examples of these organisms include AmpC β-lactamase and extended-spectrum β-lactamases (ESBLs)-producing *Enterobacteriaceae*, carbapenem-resistant Enterobacteriaceae (CRE), and multidrug-resistant (MDR) *Pseudomonas aeruginosa* [10,11]. Etiological agents of UTIs, and their susceptibility patterns vary between regions and geographical locations. Besides, the etiology and drug resistance change over time [12].

In addition, management of UTI in the era of antimicrobial resistance requires a systematic approach to diagnose the type of infection and to select the optimal dose, route, and duration of the antibiotic regimen. Unfortunately, standardized evidence-based clinical management is often lacking in general practice [13].

King Saud University Medical City (KSUMC) established its own Antimicrobial Stewardship Program (ASP). It was designed based on a thorough review of the literature, international guidelines, local antibiogram(s), and the consultation of external experts outside of the hospital as deemed necessary. It is to be used as guidance for all prescribing physicians at the health care facilities of KSUMC. Restricted antimicrobial agents will require proper approval of consultants of infectious diseases within 48 hours of initiating the prescription. Antimicrobial resistance may be associated with recurrent UTIs which hard to treat. Several studies examined the prevalence of multi-drug resistance organisms in UTIs [14-16].

Despite an increasing prevalence of antimicrobial-resistant pathogens, the pattern of bacterial resistance has not been fully studied, especially in Saudi Arabia [17,18]. The aim of this study is characterize the etiology and antimicrobial susceptibility of microorganisms causing UTI among patients attending KSUMC, and report the most common causative organisms associated with the emergence of antimicrobial resistance by age, gender, ward, comorbidity, recurrence and immune status. The results of this study will be used to create a program to control antibiotic use and reduce the emergence of bacterial resistance

Methodology

Study Setting

This study was conducted in a major tertiary hospital, the KSUMC (formerly known as King Khalid University Hospital), Riyadh, Saudi Arabia. This hospital receives referral services from nearby health centers, private hospitals, and clinics. Approval from the Institutional Review Board IRB of KKUH was obtained (protocol number 15/0391/IRB in October 29, 2015).

Study Design

A cross sectional retrospective study assessing all urine samples of patients who are suspected to have a UTI and sent to microbiology lab for culture and sensitivity, collected during the period from 16 May 2015 to the 21 February 2016. The demographic data of patients, clinical data including (patient setting, comorbidity, duration of treatment, recurrence and immune status), the organism isolated and the antimicrobial susceptibility profiles were collected from the Electronic Medical Record (EMR) using a standard data collection sheet.

Isolation and Identification of Bacterial Uropathogens

As the standard laboratory operation procedures show, clean-catch midstream morning urine specimens were collected using sterile wide mouth glass containers. Identification of organism and antimicrobial susceptibility testing were carried out by the MicroScan Walkaway 96 plus System (Beckman Coulter Diagnostics, Pasadena CA, United State of America) [19]. ESBL screening was carried out by both double disk and E-test according to the Clinical and Laboratory Standards Institute (CLSI), 2015 recommended guidelines [19]. A significant bacterium was considered if urine culture yield is $\geq 10^5$ CFU/mL [20]. Negative urine samples were excluded from the study.

Antimicrobial susceptibility tests

Antibiotic susceptibility using the Kirby-Bauer method was carried out on Mueller-Hinton agar with commercially available disks (Oxoid, Hampshire, United Kingdom) in accordance with CLSI guidelines [19].

Descriptive analysis was carried out to describe the data. Mean and standard deviation was used to describe continuous variables. Frequency and percentage was used to describe the categorical variables. All statistical analyses were carried out using SPSS, v.22.0 (IBM Corp., Armonk, NY).

Results

During the study period the microbiology lab processed 23,342 urine isolates of which 1918 samples were positive for uropathogens. Among these positive isolates 1393 (73 %) belonged to females and 525 (27 %) belonged to males. Patients were categorized into 4 different age groups and the UTI rate was higher in patient who are older than 50 years old compared to other age groups. Demographics, comorbidities, risk factors, patient setting and type of UTI are displayed in Table 1 and were categorized in accordance to gender.

The most common microbial agent leading to UTI was *E. coli* 52% (n = 997) followed by *K. pneumoniae* 15% (n = 294), *P. aeruginosa* 8% (n = 149) *S. agalactiae* 7% (n = 138), and *Enterococcus Fecalis* 5% (n = 95) as shown in Figure 1. Moreover, these were the most common microorganism isolated in all age-groups. No significant difference was found between isolated organism and age of the patients. *E. coli* and *S. agalactiae* was more frequent in women, while *K. pneumoniae* and *P. aeruginosa* was more frequent in men. Forty-two percentage of patients affected by *P. aeruginosa* experienced a recurrent UTI, compared to seventeen and eighteen percent of patients with *E. coli* and *K. pneumoniae* respectively.

Figure 1. The frequency of microorganisms isolated from the urine samples.

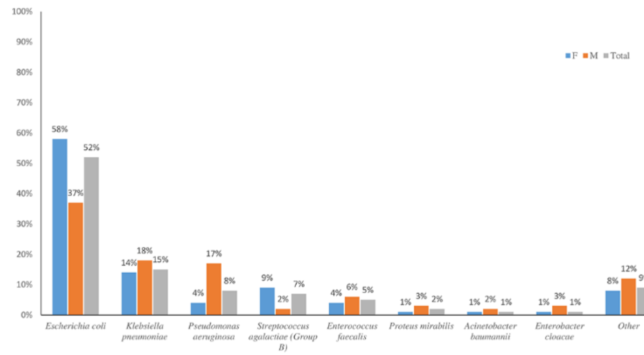

Table 1. Characteristics of patients with urinary tract infection included in this study.

Variables	Male N (%) 525 (27)	Female N (%) 1393 (73)	Total N (%) 1918 (100)
Age			
Median (in years)	53 (SD+/-28.6)	40 (SD+/-23.3)	43 (SD+/-24.9)
Age Groups			
< 18	140(27)	259(19)	399(21)
18-24	22(4)	73(5)	95(5)
25-49	89(17)	505(36)	594(31)
> 50	274(52)	556(40)	830(43)
Type of UTI			
Complicated	510(97)	1062(76)	1572(82)
Uncomplicated	15(3)	331(24)	346(18)
Recurrence			
YES	133(25)	222(16)	355(19)
NO	392(75)	1167(84)	1559(81)
Risk factors			
Anatomic abnormality	1(0.2)	6(0.3)	7(0.4)
Benign Prostatic Hyperplasia	39(7)	0	39(2)
Children	84(16)	207(12)	291(15)
Chronic Kidney Disease	31(6)	58(4)	89(5)
Diabetes	197(34)	334(24)	531(28)
Dyslipidemia	61(12)	195(14)	256(13)
Hypertension	203(39)	328(24)	531(28)
Immunosuppressant	9(2)	25(2)	34(2)
Pregnancy	0	198(14)	198(10)
Recent antimicrobial use	15(3)	30(2)	45(2)
Recent instrumentation	28(6)	17(1)	45(2)
Others	67(13)	190(14)	257(13)
Setting			
Inpatient	75(14)	456(33)	531(28)
Outpatient	449(86)	938(67)	1387(72)

SD = standard deviation.

Table 2. Resistance rates of uropathogens from culture positive urine samples to commonly used antibiotics.

	Ceftaz	Cefo	Cefep	Cefaz	Cefox	Cefur	Amp	Amox/Cla	Pip	Pip/Tazo	Erta	Tobra	Amik	Gent	Cipro	Levo	Moxi	Nor	Nitro	SXT
Non-ESBL-producing uropathogens																				
Gram-negative																				
Escherichia coli (n = 771)	30%	29%	29%	30%	10%	31%	65%	22%				11%	1%	15%	34%	28%			3%	47%
Klebsiella pneumoniae (n = 240)	26%	24%	23%	27%	11%	30%	97%	21%				9%	1%	11%	13%	7%			15%	35%
Pseudomonas aeruginosa (n = 149)	9%	36%	8%	1%	1%	0%	1%	0%				3%	1%	7%	13%	11%			40%	3%
Enterobacter cloacae (n = 28)	36%	39%	21%	82%	96%	64%	86%	86%				7%	4%	7%	11%	11%			39%	32%
Acinetobacter baumannii (n = 28)	29%	39%	43%	0%	7%	4%	7%	7%				39%	25%	39%	46%	43%			50%	25%
Proteus mirabilis (n = 29)	0%	10%	3%	28%	21%	21%	62%	24%				31%	3%	34%	31%	17%			69%	55%
Gram-positive																				
Streptococcus agalactiae (n = 138)	0%	0%	0%	0%	0%	0%	1%	0%				0%	0%	0%	3%	3%			0%	14%
Enterococcus faecalis (n = 95)	0%	0%	0%	0%	0%	0%	2%	0%				0%	0%	1%	19%	16%			1%	0%
Enterococcus faecium (n = 9)	0%	0%	0%	0%	0%	0%	78%	0%				0%	0%	0%	78%	78%			44%	0%
Staphylococcus epidermidis (n = 9)	0%	0%	0%	0%	89%	0%	44%	67%				0%	0%	33%	78%	78%			0%	44%
Others (n = 142)	1%	0%	5%	3%	32%	7%	22%	3%				9%	1%	13%	40%	8%			3	0
ESBL producing uropathogens																				
Escherichia coli (n = 226)	100%	100%	100%	100%	16%	100%	100%	55%	100%	3%	0%	29%	1%	28%	67%	61%	69%	0%	5%	65%
Klebsiella pneumoniae (n = 54)	100%	100%	100%	100%	17%	98%	100%	69%	98%	7%	7%	37%	2%	37%	37%	17%	48%	0%	22%	85%

Ceftaz: Ceftazidime; Cefo: Cefoperazone; Cefep: Cefepime; Cefaz: Cefazolin; Cefox: Cefoxitin; Cefur: Cefuroxime; Amp: Ampicillin; Amox/Clav: Amoxicillin/ Clavulanate; Tobra: Tobramycin; Amik: Amikacin; Gent: Gentamicin; Cipro: Ciprofloxacin; Levo: Levofloxacin; Nitro: Nitrofurantoin; SXT: Sulphamethoxazole/trimethoprim; Pip: piperacillin; Pip/Taz: Pipercillin/Tazobactam; Ert: Ertapenem; Mox: Moxifloxacin; Nor: Norfloxacin.

Being the most common causative UTI agents, *E. coli* showed highest resistance to ampicillin (65%), followed by sulfamethoxazole/trimethoprim (47%) and ciprofloxacin (34%), while *K. pneumoniae* showed highest resistance to ampicillin (97%) sulfamethoxazole/trimethoprim (35%) followed by cefuroxime (30%) and *P. aeruginosa* showed highest resistance to nitrofurantoin (40%) followed by cefotaxime (35%) (Table 2). The gram positive organism *Enterococcus faecium* showed a high resistant (78%) to ampicillin, levofloxacin and ciprofloxacin, while *Staphylococcus epidermidis* had a high rate of resistance to cefotaxime (89%), amoxicillin/clavulanate (67%), levofloxacin (78%) and ciprofloxacin (78%).

ESBL producing uropathogens constituted 15% (n = 293). The most common ESBL producing uropathogens were *E. coli*, *K. pneumoniae*, *Citrobacter amalonaticus*, *Enterobacter aerogenes* and *E. cloacae*. ESBL-producing *E. coli* was isolated from urine culture in 226 of the cases and *K. pneumoniae* in 54 of the cases. The majority of ESBL-producing *E. coli* were resistance to ceftazidime, cefotaxime, levofloxacin and ciprofloxacin. However, they were highly susceptible to carbapenems, amikacin and piperacillin/tazobactam. On the other hand, the ESBL-producing *K. pneumoniae* showed highest resistance rate to piperacillin, cefotaxime and ceftazidime while ciprofloxacin and levofloxacin had a lower resistant rate compared to ESBL-producing *E. coli*.

Discussion

The most common causative organisms of UTI in our study were *E. coli* (52%) followed by *K. pneumoniae* (15%), *P. aeruginosa* (8%), *S. agalactiae* (7%), and *E. faecalis* (5%). Our results are consistent with epidemiological data locally and globally. In the United States, *E. coli* accounts for 65% and 75% of complicated and uncomplicated UTIs respectively, followed by *E. faecalis* (11%) and *K. pneumoniae* (8%) in complicated UTIs, and by *K. pneumoniae* (6%), *S. saprophyticus* (6%) and *E. fecalis* (5%) in uncomplicated UTIs [21]. In general, uncomplicated UTI is common in young females or older patients of either gender, while complicated UTI is commonly encountered in patients with indewlling catheters, immunosupression, urinary tract abnormalities, or recent antbiotic exposure. *E. coli*, *K. pneumoniae*, and *P. aeruginosa* are the most common identified uropathogens in Saudi Arabia [22,23].

Despite of lack of significant difference between isolated organisms across different ages, most of the causative uropathogens in our study were more frequent (43%) in patient older than 50 years compared to other age groups (< 18 years old with 21%; 18-24 years old with 5%; 25-49% with 31%) . These findings are different from an old study conducted by Eltahawy, who found that more than 50% of patients with bacteriuria were in the age group of 21-50, but consistent with the most recent studies who found that more than 50% uropathogens-causing bacteriuria are detected in patients older than 50 years old [22-24].

In our study, females represented 73% of all identified UTIs with *E. coli* and *S. agalactiae* being the most frequently isolated uropathogens, while *K. pneumonia* and *P. aeruginosa* were more frequent in males. In a study conducted by Almijalli, females were more prone for UTIs than males untill the age of 50 years, with *E. coli* being the most frequently isolated organism in females and males (50% and 28.5% respectively); however, *K. pneumonia* was more often found in males than females [25].

E.coli is considered the main causative organism of recurrent UTI, especially in women. It is estimated to be responsible for almost 80% of the recurrent cases [26]. Recurrent UTI in our study, which was identified if the patient has two or more positive urine cultures during the study period, was more associated with patients who were infected by *P. aeruginosa* (42%) more than *E. coli* (17%) or *K. pneumonia* (18%). The microbiological difference in the incidence of recurrent UTI between our study and published literature may be explained by the fact that our study identified the prevalence of causative and resistant uropathogens from laboratory sight. However, the high percentage of *P. aeruginosa* involvement in recurrent UTI raises the concern of its role in the recurrent UTI in future studies.

Of the common prescribed antibiotics for UTI management, the two common identified causative uropathogens in this study, *E. coli* and *K. pneumonia*, showed the highest resistance to sulfamethoxazole/trimethoprim (82%), followed by cefuroxime (61%), ciprofloxacin (47%), amoxicillin/ clavulanate (43%), levofloxacin (35%), and nitrofurantoin (17%).

Of the first defense prescribed antibiotics for UTI, *E. coli* was most commonly resistant to Sulfamethoxazole/Trimethoprim (47%) followed by ciprofloxacin (34%). *K. pneumoniae* was most often resistant to Sulfamethoxazole/trimethoprim (35%) followed by cefuroxime (30%), while *P. aeruginosa* was most commonly resistant to ciprofloxacin (13%).

E. Coli & K. pneumonia resistant strains to sulfamethoxazole/trimethoprim are often associated with acquisition of the resistance genes such dfr, sul1 or sul2-gene, or presence of integron class I or II [27,28]. Cefuroxime resistance mechanisms in K. pneumonia may be realted to the release of ESBLs and down-regulation of porins [28]. DNA gyrase mutations, enhanced efflux activity, decreased uptake of the drug were identified as resistant mechansims of E. coli towrads fluoroquinolones [29]. Gene mutation is considered the essential resistant-mechanism for *P. aeruginosa* against cephalosporin [28].

Similar results were found in a Saudi study conducted in a tertiary hospital to investigate the microbiological causes and antibiotic sensitivity of 116 outpatient urine samples [25]. In that study, *E. coli* showed 70.33% and 62.64% resistance to sulfamethoxazole/trimethoprim and ciprofloxacin, respectively, while *K. pneumoniae* showed 70% and 28% resistance to sulfamethoxazole/trimethoprim and ciprofloxacin, respectively.

The high incidence of resistant pathogens to the first-line therapy is contributed to several factors such as antibiotic misuse or using antibiotics without prescrition. Although, there is no well-defined study assesses the antbiotic utlilization in Saudi Arabia due to the poor practice of documentation and missing of definite diagnosis, a study conducted in a western region found that antibiotics prescription was accounted for 46% of all prescribed medications in the emergency department [30]. This is high percentage perceeds the World Health Orgnization (WHO) acceptable percentage (15-20%) of antibiotics prescription in the countries where an infectious disease is prevalent [31]. Self-medication with antbiotics is an essential dilemma in Saudi Arabia where 77.6% of the pharmacies are dispensing antibiotics without prescription, and almost 79% of the citizens purchased at least one antibiotic without a prescription [32,33].

Although emergence of antibiotic resistance may differ regionally and geographically, our results seem consistent with the global data of antibiotic resistance in urine isolates. *E. coli* that was isolated from 12 million urine samples from 2000 to 2010 in the United States showed accelerated rates of resistance towards ciprofloxacin and sulfamethoxazole/trimethoprim [34]. During this period, the incidence of *E. coli* resistance towards ciprofloxacin increased 5 fold from 3% to 17.1% while the resistance towards sulfamethoxazole/trimethoprim increased from 17.9% to 24.2%. Based on our results and previous studies in the region, nitrofurantoin has the best susceptibility profile to UTI caused by *E. coli* and *K. pneumoniae*; however, recommending nitrofurantoin as first line empirical therapy needs further research on the classification and severity of UTI, and microbiological data and antibiotic susceptibility based on the classification and severity [35-37].

The incidence of ESBL-producing *Enteriobactercieae* has increased dramatically in different countries [36-39]. The prevalence of ESBL-producing *E.coli* is higher than ESBL-producing *K. pneumoniae.* It is estimated that the prevalence of ESBL-producing *E. coli* is 11% in Europe and from 5.28 to 10.5 patients per 100,000 patients in the United States [35,36]. The prevalence of ESBL-producing *E. coli* has been increasing in different parts of Asia including Saudi Arabia [38]. Currently, Asia is known to have some deadly ESBL-producing pathogens such as *Klebsiella pneumoniae* carbapenemase, and New Delhi metallo-β-lactamase (NDM)-producing *E. coli*. Increasing trends in ESBL-producing pathogens, mostly *E. coli* and *K. pneumoniae* have been noted in Saudi Arabia. Some Studies have suggested that the prevalence of ESBL-producing *Enterobacteriaceae* has been increased from 4.8% in 2003 to 9.6% in 2004 in Saudi Arabia, of which ESBL producing *E. coli* accounts for 38.8% [39-41].

Our results are consistent with these local and global increasing trends in ESBL-producing pathogens. Of the 1918 urine isolates we collected during the period from May 2015 to February 2016, ESBL-producing uropathogens were identified in 15.2% (n = 293). The most common ESBL producing organism were *E. coli* (n = 226) and *K. pneumoniae* (n=54). Increasing trends in ESBL-producing pathogens has been noted globally. The incidence of ESBL-producing *E. coli* increased significantly in the United States from 5.28 patients per 100,000 patients in 2008 to 10.5 patients per 100,000 patients in 2014 [37,38]. A similar noticeable increase in the prevalence of ESBL-producing *E. coli* was seen in Spain from 8% in 2008 to 12% in 2010 [42].

The majority of ESBL-producing *E. coli* were resistant to third generation cephalosporins and fluoroquinolones, but highly susceptible to carbapenems amikacin, and piperacillin/tazobactam. Similar resistance patterns of ESBL-producing *E. coli* in urine isolates were identified in another study where urine-collected samples were resistant to third generation cephalosporins and fluoroquinolones in approximately 33% and 55% of the cases respectively. Samples were highly sensitive to Carbapenems, amikacin, and piperacillin/tazobactam in approximately 100%, 80%, and 91% respectively [43].

Conclusion

Our results further enhance research into the prevalence of classification and severity of UTIs, microbiological data and antibiotic susceptibility based on classification and severity. Also, the increasing prevalence of the most common uropathogens towards the most prescribed antibiotics, and the accelerated growth of ESBL-producing pathogens, should be thoroughly investigated because the use of inappropriate antibiotics may further worsen the situation. Although our study is a retrospective study focusing on laboratory reporting and healthcare provider documentation, it included high number of urine isolates and reports data that has not been reported in such numbers and manner locally. Our study investigated the most common causative and resistant uropathogens within a community teaching hospital. These findings highlight the importance of formulating local empirical guidelines and having antimicrobial stewardship programs to promote the ideal use of antibiotics.

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References

1. Dalela G, Gupta S, Jain DK, Mehta P (2012) Antibiotic resistance pattern in uropathogens at a tertiary care hospital at Jhalawar with special reference to Esbl, Ampc β-Lactamase and MRSA production. J Clin Diagn Res 6: 645-651.
2. Gupta K, Hooton TM, Naber KG, Wullt B, Colgan R, Miller LG, Moran GJ, Nicolle LE, Raz R, Schaeffer AJ, Soper, DE (2011) International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: A 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. Clin Infect Dis 52: e103-e120.
3. Kashef N, Djavid GE, Shahbazi S (2010) Antimicrobial susceptibility patterns of community-acquired uropathogens in Tehran, Iran. J Infect Dev Ctries 4: 202-206. https://dx.doi.org/10.3855/jidc.540.
4. Foxman B (2002) Epidemiology of urinary tract infections: incidence, morbidity, and economic costs. Am J Med 113: 5-13.
5. Aly MM, Balkhy H (2012) The prevalence of antimicrobial resistance in clinical isolates from Gulf Corporation Council countries. Antimicrob Resist Infect Control 1: 26.
6. Banerjee S (2009) The Study of Urinary Tract Infections and antibiogram of uropathogens in and around Ahmadnagar, Maharashtra. Internet J Infect Dis 9: 1-5.
7. Leegaard TM, Caugant DA, Froholm LO, Hoiby EA (2000) Apparent difference in antimiovrobial susceptibility as a consequence of national guidelines. Clin Microbiol Infect 6: 290-293.
8. Warren JW, Abrutyn E, Hebel JR, Johnson JR, Schaeffer AJ, Stamm WE (1999) Guidelines for antimicrobial treatment of uncomplicated acute bacterial cystitis and acute pyelonephritis in women. Infectious Diseases Society of America (IDSA). Clin Infect Dis 29:745–758.
9. Sood S, Gupta R. Antibiotic resistance pattern of community acquired uropathogens at a tertiary care hospital in Jaipur, Rajasthan (2012) Indian J Community Med 37: 39-44
10. De Francesco MA, Ravizzola G, Peroni L, Negrini R, Manca N (2007) Urinary tract infections in Brescia, Italy: Etiology of uropathogens and antimicrobial resistance of common uropathogens. Med Sci Monit 13: 136-144
11. Linhares I, Raposo T, Rodrigues A, Almeida A (2013) Frequency and antimicrobial resistance patterns of bacteria implicated in community urinary tract infections: a ten-year surveillance study (2000-2009). BMC Infect Dis 13: 19.
12. Hirsch EB, Zucchi PC, Chen A, Raux BR, Kirby JE, McCoy C, Eliopoulos GM (2016) Susceptibility of multi drug resistant gram-negative urine isolates to oral antibiotics. Antimicrob Agents Chemother 60: 3138–3140.
13. Ironmonger D, Edeghere O, Gossain S, Hawkey PM (2016) Use of antimicrobial resistance information and prescribing guidance for management of urinary tract infections: survey of general practitioners in the West Midlands. BMC Infect Dis 16: 226.
14. Gupta S, Kapur S, Padmavathi D (2014) Comparative Prevalence of Antimicrobial Resistance in Community-Acquired Urinary Tract Infection Cases from Representative States of Northern and Southern India. J Clin Diagn Res 8: DC09-12.
15. Sanchez G, Baird A, Karlowsky J, Master R, Bordon J (2014) Nitrofurantoin retains antimicrobial activity against multidrug-resistant urinary *Escherichia coli* from US outpatients. J Antimicrob Chemother 69: 3259-3262.
16. Stefaniuk E, Suchocka U, Bosacka K, Hryniewicz W (2016) Etiology and antibiotic susceptibility of bacterial pathogens responsible for community-acquired urinary tract infections in Poland. Eur J Clin Microbiol Infect Dis 35: 1363-1369.
17. Al-Rubeaan K, Moharram O, Al-Naqeb D, Hassan A, Rafiullah M (2012) Prevalence of urinary tract infection and risk factors among Saudi patients with diabetes. World J Urol 31: 573-578.
18. Al-Harthi, AA, Al-Fifi SH (2008) Antibiotic resistance pattern and empirical therapy for urinary tract infections in children. Saudi Med J 29: 854-858.
19. Clinical and Laboratory standard institute (CLSI) (2015) Performance standards for antimicrobial susceptibility testing, 25th informational supplement. CLSI document M100-S25 (ISBN 1-56238-990-4).
20. Cheesbourgh M (1986) Medical laboratory manual for tropical countries, 2nd edition. London: Butterworth-Heineman Ltd 624 p.
21. Flores-Mireles AL, Walker JN, Caparon M, Hultgren SJ (2015) Urinary tract infections: epidemiology, mechanisms of infection and treatment options. Nat Rev Microbiol 3: 269-284.
22. Ahmad S, Ahmad F (1995) Urinary tract infection at a specialist hospital in Saudi Arabia. Bangladesh Med Res Counc Bull 21: 95-98.
23. Alzohairy M, Khadri H (2011) Frequency and antibiotic susceptibility pattern of uro-pathogens isolated from community and hospital-acquired infections in Saudi Arabia - A prospective case study. Brit J Med Med Res 1: 45-56.

24. Eltahawy A, Khalaf R (1988) Urinary tract infection at a university hospital in Saudi Arabia: Incidence, microbiology, and antimicrobial susceptibility. Ann Saudi Med 8: 261-266.
25. Al-Mijalli SHS (2017) Bacterial uropathogens in urinary tract infection and antibiotic susceptibility pattern in Riyadh Hospital, Saudi Arabia. Cell Mol Med 3: 1.
26. Tadesse D A, Zhao S, Tong E, Ayers S, Singh A, Bartholomew M J, McDermott P F (2012). Antimicrobial drug resistance in *Escherichia coli* from humans and food animals, United States, 1950–2002. Emerg Infect Dis 18: 741-749.
27. Brolund A, Sundqvist M, Kahlmeter G, Grape M (2010) Molecular characterization of trimethoprim resistance in *Escherichia coli* and *Klebsiella pneumoniae* during a two year intervention on trimethoprim use. PLoS ONE 5: e9233.
28. Källman O, Motakefi A, Wretlind B, Kalin M, Olsson-Liljequist B, Giske CG (2008) Cefuroxime non-susceptibility in multidrug-resistant *Klebsiella pneumoniae* overexpressing ramA and acrA and expressing ompK35 at reduced levels. J Antimicrob Chemother 62: 986–990.
29. Su HC, Ramkissoon K, Doolittle J, Clark M, Khatun J, Secrest A, Wolfgang MC, Giddings MC (2010) The development of ciprofloxacin resistance in *Pseudomonas aeruginosa* involves multiple response stages and multiple proteins. Antimicrob Agents Chemother 54: 4626-4635.
30. Oqal MK, Elmorsy SA, Alfhmy AK, Alhadhrami RM, Ekram RA, Althobaiti IA, Ghoneamy SS (2015) Patterns of antibiotic prescriptions in the outpatient department and emergency room at a Tertiary Care Center in Saudi Arabia. Saudi J Med Med Sci; 3: 124-129.
31. Action Program on Essential Drugs and Vaccines (World Health Organization) (1993) How to Investigate Drug Use in Health Facilities: Selected Drug Use Indicators. Geneva: Action Program on Essential Drugs. Available: http://apps.who.int/medicinedocs/pdf/s2289e/s2289e.pdf Accessed 21st January 2018.
32. Bin Abdulhak AA, Altannir MA, Almansor MA, Almohaya MS, Onazi AS, Marei MA, Aldossary OF, Obeidat SA, Obeidat MA, Riaz MS, Tleyjeh IM (2011) Non prescribed sale of antibiotics in Riyadh, Saudi Arabia: a cross sectional study. BMC public health 11: 538.
33. AlRasheed A, Yagoub U, Alkhashan H, Abdelhay O, Alawwad A, Al Aboud A, Al Battal S (2016). Prevalence and predictors of self-medication with antibiotics in Al Wazarat health center, Riyadh City, KSA. Biomed Res Int Available: http://dx.doi.org/10.1155/2016/3916874. Accessed 8 May 2017.
34. Sanchez GV, Master RN, Karlowsky JA, Bordon JM (2012) *In vitro* antimicrobial resistance of urinary *Escherichia coli* isolates among U.S. outpatients from 2000 to 2010. Antimicrob Agents Chemother 56: 2181-2183.
35. Hawser SP, Bouchillon SK, Lascols C, Hackel M, Hoban DJ, Badal RE, Cantón R (2012) Susceptibility of European *Escherichia coli* clinical isolates from intra-abdominal infections, extended-spectrum betalactamase occurrence, resistance distribution, and molecular characterization of ertapenem-resistant isolates (SMART 2008–2009). Clin Microbiol Infect 18: 253–259.
36. Freeman JT, Sexton DJ, Anderson DJ (2009) Emergence of extended-spectrum beta-lactamase-producing *Escherichia coli* in community hospitals throughout North Carolina: a harbinger of a wider problem in the United States? Clin Infect Dis 49: e30–e32.
37. Thaden JT, Fowler VG, Sexton DJ, Anderson DJ (2016) Increasing incidence of extended-spectrum β-lactamase-producing *Escherichia coli* in community hospitals throughout the Southeastern United States. Infect Control Hosp Epidemiol 37: 49-54.
38. Sidjabat HE, Paterson DL (2015) Multidrug-resistant Escherichia coli in Asia: epidemiology and management. Expert Rev Anti Infect Ther 13(5):575-591.
39. Kader AA, Kumar AK (2004) Prevalence of extended spectrum beta-lactamase among multidrug resistant gram-negative isolates from a general hospital in Saudi Arabia. Saudi Med J 25:570-4.
40. Kader AA, Angamuthu K (2005) Extended-spectrum beta-lactamases in urinary isolates of Escherichia coli, Klebsiella pneumoniae and other gram-negative bacteria in a hospital in Eastern Province, Saudi Arabia. Saudi Med J 26:956-959.
41. Hassan H, Abdalhamid B (2014) Molecular characterization of extended-spectrum beta-lactamase producing Enterobacteriaceae in a Saudi Arabian tertiary hospital. J Infect Developing Ctries 8:282-288.
42. European Antimicrobial Resistance Surveillance Network (EARS-Net). (Accessed Dec 3, 2017) Available from: http://www.ecdc.europa.eu/en/activities/surveillance/EARS-Net/Pages/index.aspx.
43. Kumar D, Singh AK, Ali MR, Chander Y (2014) Antimicrobial Susceptibility Profile of Extended Spectrum β-Lactamase (ESBL) Producing Escherichia coli from Various Clinical Samples. Infect Dis (Auckl) 7:1-8.

Corresponding author
Wael Mansy
Assistant Professor
Clinical Pharmacy Department, College of Pharmacy, King Saud University, PO Box 2457, Riyadh 11451, Saudi Arabia.
Phone: +966567253275.
Fax: +966 114677480.
E mail: wsayed@ksu.edu.sa

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