Research Article

Prevalence and Antimicrobial Resistance of Urinary Tract Infections in Upper Egypt

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Abstract
Background: Urinary tract infections (UTIs) are among the commonest infections both in community and hospitals that showed emergence of multidrug resistance which is challenging UTI treatment. This study aimed to detect the prevalence of UTI, describe clinical presentations of UTI patients and define different bacterial uropathogens and antimicrobial susceptibility patterns of isolated Enterobacteriaceae species. **Materials and Methods**: From July 2016 to March 2017; 1353 urine specimens were collected from outpatients and inpatients presented to Minia university hospitals, Minia, Egypt. Demographic and clinical data of subjects were collected. Uropathogens were isolated on UTI chromogenic media and identified according to their phenotypic criteria, antimicrobial susceptibility was performed using disk diffusion method. **Results**: UTI prevalence was 52.1% which was more prevalent among married adult females from rural communities with 78.3% of subjects had one or more risk factors for UTI. Enterobacteriaceae prevalence, with *E-coli* being the most frequently isolated, was 62.4% among isolated uropathogens, 31.1% of them showed multidrug resistance (MDR). The highest rate of resistance was against sulfamethoxazole-trimethoprim (57.5%), Ceftriaxone (49.3%) and Amoxicillin clavulanic acid (36.1%) and highest susceptibility rate was found to Imipenem (100%). **Conclusion**: UTIs are common among Egyptian population and emergence of MDR Enterobacteriaceae strains among isolated uropathogens can lead to treatment failure. Proper antimicrobial polices and control of risk factors can lead to better management of UTIs.
Keywords: UTI, Enterobacteriaceae, *E-coli*, MDR

Introduction
Urinary tract infection (UTI) is defined as microbial colonization of urine with tissue invasion of any structure of the urinary tract. Community-acquired UTI (CAUTI) prevalence is 0.7% worldwide while Healthcare-associated UTI (HAUTI) frequency among HCAIs is 12.9, 19.6 and 24% in the United States, Europe and developing countries, respectively (Tandogdu et al, 2016). UTI accounts for 15% of HCAIs in Egypt (Talaat et al., 2016).

According to CDC criteria for diagnosis of symptomatic urinary tract infection; UTI can be diagnosed if the patient has at least one of the following clinical symptoms or signs; fever ≥38°C, suprapubic pain, costovertbral angle pain, urinary urgency, frequency or dysuria together with a urine culture with no more than two species of organisms identified; at least one of them is a bacterium of $\geq 10^5$ CFU/ml (CDC, 2018). Different risk factors favor development of UTI as diabetes, immunosuppression, urogenital abnormality, history of administration of antimicrobials and catheterization (Vasudevan, 2014).

UTIs are classified according to source of infection into hospital acquired urinary tract infection (HA-UTI) which affect inpatients after 48 hours of admission, and community acquired urinary tract infection (CA-UTI) which occurs in patients visiting the hospital on an outpatient basis or admitted for lesser than 48 h (Nishat et al, 2014). Enterobacteriaceae members are major causative agents in both CA-UTI (Malmartel & Ghasarossian, 2016 and Park et al., 2017) and HA-UTI; Ponce-de-Leon et al., 2018.

UTIs are caused by both Gram-negative and Gram-positive bacteria; the most common causative agent is uropathogenic *Escherichia coli* (UPEC). Other agents involved in UTIs are *Klebsiella pneumoniae*, *Staphylococcus saprophyticus*, *Enterococcus faecalis*, group B

Streptococcus (GBS), *Proteus mirabilis*, *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Candida* spp. (Flores-Mireles et al., 2015).

Widespread use of antibiotics that are given empirically without proper antibiotic susceptibility testing was a leading cause in emergence of MDR strains isolated from UTIs. So, to ensure appropriate therapy, current knowledge of the organisms that cause UTIs in the locality and their antimicrobial suscepti-bility is extremely important (Mazzariol et al., 2017).

Materials and Methods

Ethical considerations: The study protocol was approved by the local institutional review board at the authors' affiliated institution and consent was obtained from all the study participants.

Study design: 1353 urine specimens were collected from outpatients and inpatients presented to Minia university hospitals during the period from July 2016 to March 2017, inpatients were included after 48 hours of admission and outpatients who attended at outpatient clinics were included. Adult (≥ 18 years) only were included. Demographic and clinical data of study subjects were collected.

Sample collection: A clean catch midstream morning urine specimen was obtained from non-catheterized patients (Tille, 2014) and from catheterized patients via aspiration by a needle (Mgoldrick, 2015). Each specimen was collected in a sterile screw capped container, transported to microbiology laboratory within two hours of collection in an icebox and processed at once.

Culture and Identification: urine specimens from symptomatic patients were streaked by semi-quantitative streaking method onto UTI chrome agar (CHROMagar™ Orientation, paris, france); figure 1 and by calibrated loop technique on MacConkey and blood agars (Tille, 2014) . Isolated uropathogens with a colony count $\geq 10^5$ CFU/ml were further identified according to their phenotypic criteria; based on gram staining, cultural characters and biochemical testing. A total of 705 pure bacterial isolates; corresponding to 705 UTI patients were obtained.

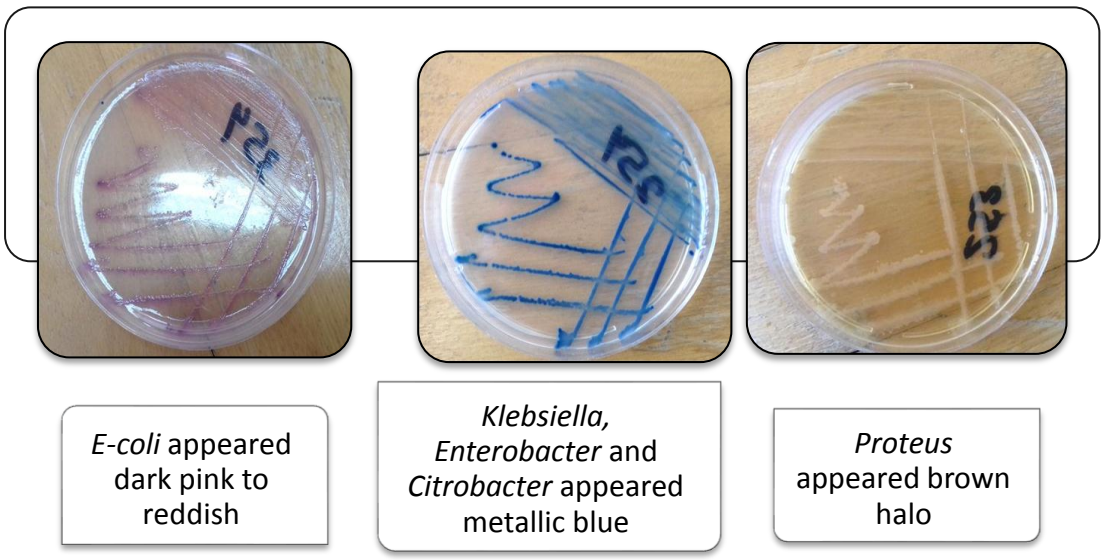

Figure 1: Different Enterobacteriaceae isolates on UTI chromogenic media

Antimicrobial susceptibility testing:

According to CLSI guidelines **(CLSI, 2015)** ;disk diffusion method was used to determine antimicrobial susceptibility of the Entero-bacteriaceae isolates to different antibiotics (Thermo Scientific™ Oxoid, UK); Amoxicillin/ clavulanic acid (AMC) 30µg, Ceftriaxone (CRO) 30µg, Ceftazidime (CAZ) 30µg, Imipenem (IPM) 10µg, Amikacin (AK) 30µg, Sulphamethoxazole/Trimethoprim (SXT) 25µg, Nalidixic acid (NA) 30 µg, Ciprofloxacin (CIP) 5µg, Norfloxacin (NOR) 10µg, Ofloxacin (OFX) 5µg and Nitrofurantoin (F) 300 µg.

Results were interpreted according to CLSI guidelines **(CLSI, 2016)**

Statistical analysis of demographic, clinical and laboratory data of study subjects was performed using SPSS for Windows version 19.0 (IBM, USA).

Results

The study revealed 705 patients with symptomatic urinary tract infection that were diagnosed according to CDC criteria; with a prevalence of 52.1% of the investigated population. Two groups of patients were enrolled in the study; outpatients' group which represent CA-UTI accounted for 59.4% (419) of study patients. The inpatients' group which represent HA-UTI accounted for 286 (40.6%) patients.

Patients' characteristics: UTI prevalence was the highest among young adults (18-29 years) and in females (67.8%) than males (32.2%) and in married subjects (78.9%) rather than unmarried (21.1%). The infection was more prominent in individuals from rural areas (62.6%) and in unemployed individuals (56.3%); Table 1.

Clinical history data of subjects: symptoms and signs of UTI were investigated; dysuria was the most frequent complaint followed by increased frequency of micturition and suprapubic pain and all of these symptoms were more abundant among outpatient population. At general, fever (43.4%) was the least recorded clinical sign but it was the second common finding among inpatients with a percentage of 71% of them. Other clinical data together with symptoms and signs are illustrated in table 2.

Identification of isolates: Enterobacteriaceae species with *E-coli* being the most frequently isolated pathogen accounted for 62.4% (440/ 705) of study isolates obtained from urine culture; two hundred and nine (73.1%) from inpatients and 231 (55.1%) from outpatients. Gram positive cocci accounted for 37.6% (265/705) of isolates, being more isolated from outpatients. Frequency of different species among study isolates is illustrated in table 3.

Antimicrobial susceptibility pattern of Enterobacteriaceae isolates: Of the 440 Enterobactericeae clinical isolates tested for antimicrobial susceptibility, 137/440 (31.1%) of them showed multidrug resistance (MDR). Resistance rates are illustrated in table 4. For majority of antimicrobial classes, higher resistance rates were recorded among inpatients more than outpatients except for Nitrofurantoin as shown in table 4.

Table 1: Patients' characteristics

Characteristic		**Total (n=705)**		**Type of visit**				***P* value**
				Outpatients (n=419)		**Inpatients (n=286)**		
Age (years)	Mean±SD	38.8±12.5		36.8±12.4		41.6±12.1		**0.0001**
	Range	18-66						
Age group N (%)	18-29	246	34.9%	178	42.5%	68	23.8%	**0.0001**
	30-39	101	14.3%	62	14.8%	39	13.6%	
	40-49	189	26.8%	83	19.8%	106	37.1%	
	50-59	154	21.8%	92	22.0%	62	21.7%	
	Above 60	15	2.1%	4	1.0%	11	3.8%	
Gender N (%)	Male	227	32.2%	96	22.9%	131	45.8%	**0.0001**
	Female	478	67.8%	323	77.1%	155	54.2%	
Residence N (%)	Rural	441	62.6%	256	61.1%	185	64.7%	0.3
	Urban	264	37.4%	163	38.9%	101	35.3%	
Marital status N (%)	Married	556	78.9%	335	80.0%	221	77.3%	0.4
	unmarried	149	21.1%	84	20.0%	65	22.7%	
Occupation N (%)	unemployed	397	56.3%	288	68.7%	109	38.1%	**0.0001**
	employee	83	11.8%	43	10.3%	40	14.0%	
	handicraft	225	31.9%	88	21.0%	137	47.9%	

Table 2: Symptoms, signs and risk factors of UTI in study patients

Characteristic		Total (n=705		Type of visit				*P* value
				Outpatients (n=419)		Inpatients (n=286)		
		N	%	N	%	N	%	
Fever	Yes	306	43.4%	103	24.6%	203	71.0%	**0.0001**
	No	399	56.6%	316	75.4%	83	29.0%	
Dysuria	Yes	642	91.1%	396	94.5%	246	86.0%	**0.0001**
	No	63	8.9%	23	5.5%	40	14.0%	
Increased frequency	Yes	563	79.9%	401	95.7%	162	56.6%	**0.0001**
	No	142	20.1%	18	4.3%	124	43.4%	
Suprapubic pain	Yes	481	68.2%	307	73.3%	174	60.8%	**0.0001**
	No	224	31.8%	112	26.7%	112	39.2%	
Risk factor	Yes	552	78.3%	346	82.6%	206	72.0%	**0.001**
	No	153	21.7%	73	17.4%	80	28.0%	
Diabetes	Yes	223	31.6%	180	43.0%	43	15.0%	**0.0001**
	No	482	68.4%	239	57.0%	243	85.0%	
Urogenital abnormality	Yes	166	23.5%	130	31.0%	36	12.6%	**0.0001**
	No	539	76.5%	289	69.0%	250	87.4%	
Catheterization	Yes	163	23.1%	36	8.6%	127	44.4%	**0.0001**
	No	542	76.9%	383	91.4%	159	55.6%	
Recurrence	Yes	353	50.1%	286	68.3%	67	23.4%	**0.0001**
	No	352	49.9%	133	31.7%	219	76.6%	
History of Antimicrobials	Yes	230	32.6%	76	18.1%	154	53.8%	**0.0001**
	No	475	67.4%	343	81.9%	132	46.2%	

Table 3: Frequency of different isolated Uropathogens

Organism	Total		Outpatients		Inpatients		*P* value
	n	%	n	%	n	%	
E-coli	281	39.9%	147	35.1%	134	46.9%	**0.0001**
klebsiella	81	11.5%	40	9.5%	41	14.3%	
Citrobacter	47	6.7%	17	4.1%	30	10.5%	
Enterobacter	11	1.6%	9	2.1%	2	0.7%	
Proteus	20	2.8%	18	4.3%	2	0.7%	
Gram positive cocci	265	37.6%	188	44.9	77	26.9%	
Total	705	100%	419	59.4%	286	40.6%	

Table 4: **Antimicrobial susceptibility pattern of different isolated Enterobacteriaceae species.**

Antimicrobial agent		Total (n=705)	Outpatients n=231		Inpatients n=209		*P* value
Name	Pattern	N (%)	N	%	N	%	
AMC	sensitive	281 (63.9)	157	68%	124	59.3%	**0.03**
	resistant	159 (36.1)	74	32%	85	40.7%	
CTZ	sensitive	298 (67.7)	153	66.2%	145	69.4%	0.27
	resistant	142 (32.3)	78	33.8%	64	30.6%	
CRO	sensitive	223 (50.7)	129	55.8%	94	45.0%	0.23
	resistant	217 (49.3)	102	44.2%	115	55.0%	
IMP	sensitive	440 (100)	231	100%	209	100%	**0**
	resistant	0 (0.0)	0	.0%	0	.0%	
AK	sensitive	356 (80.9)	210	90.9%	146	69.9%	**0.0001**
	resistant	84 (19.1)	21	9.1%	63	30.1%	
SXT	sensitive	187 (42.5)	110	47.6%	77	36.8%	**0.02**
	resistant	253 (57.5)	121	52.4%	132	63.2%	
NA	sensitive	297 (67.5)	184	79.7%	113	54.1%	**0.0001**
	resistant	143 (32.5)	47	20.3%	96	45.9%	
CIP	sensitive	350 (79.5)	202	87.4%	148	70.8%	**0.0001**
	resistant	90 (20.5)	29	12.6%	61	29.2%	
NOR	sensitive	350 (79.5)	202	87.4%	148	70.8%	**0.0001**
	resistant	90 (20.5)	29	12.6%	61	29.2%	
OFX	sensitive	350 (79.5)	202	87.4%	148	70.8%	**0.0001**
	resistant	90 (20.5)	29	12.6%	61	29.2%	
F	sensitive	330 (75.0)	165	71.4%	165	78.9%	0.069
	resistant	110 (25.0)	66	28.6%	44	21.1%	

Discussion

Analysis of age, gender and marital status of UTI patients in the current study revealed that UTI is more common in married adult females which can be explained by their urogenital physiology together with presence of factors as sexual activity, pregnancy and use of certain contraception methods which encourage the infection (Vasudevan, 2014). Other studies recorded the high prevalence of UTI in females; with a percentage of 75.3% and 66.2% respectively (Jadoon, 2015 and Kibret &Abera, 2014) and also in adults (Kibret &Abera, 2014 and Gangcuangco, 2015) High percentage of rural patients (62.6%) in the current study may explain that the infection is quite common in these localities probably due to less hygienic measures. In addition; unemployed individuals (56.3%) were highly affected by UTIs which may be due to the fact that the prevalence of UTI in females is high and females in rural localities are usually housewives which agree with wong et al., 2017 who found that unemployed subjects were the majority of those complaining from UTI. On the other hand it may be linked to low income level of these individuals which agree Derese et al., 2016.

There are a number of studies that investigated risk factors for UTI. Percentage of Diabetes among UTI patients in other studies was closely to what was detected in the current study (31.6%), a percentage of 20%, 26.5%, 22% and 34.4% were reported by Khawcharoenporn et al., 2013, Yoon, 2014, Osthoff et al., 2015 and Bischoff et al., 2018 respectively. Different Urogenital abnormalities were detected in 23.5% of current study patients which is close to Khawcharoenporn et al., 2013 and Yoon, 2014 who reported percentages of 22% and 25.3% respectively among UTI patients. History of Catheterization was detected in 33%, 27.9% and 16.1% of UTI patients as denoted by Khawcharoenporn et al., 2013, Yoon, 2014 and Bischoff et al., 2018 respectively which were close to the current study results (23.1%). History of recurrence was stated by 50.1% of study patients while other studies reported

percentages of 40%, 15% and 21.9% by Khawcharoenporn et al., 2013, Osthoff et al., 2015 and Bischoff et al., 2018 respectively. History of administration of antimicrobial agents was present in 32.6% of UTI patients in the study; others recorded percentages of 27% (Khawcharoenporn et al., 2013), 70% (Osthoff et al., 2015) and 14.6% (Bischoff et al., 2018).

In the current study, 440 Enterobacteriaceae strains were isolated from UTI with a percentage of 62.4%, more frequently from inpatients (73.1%) and 55.1% of outpatients. A slightly higher frequency of isolation from UTIs (75.8%) was recorded previously in the same hospital (Gad et al., 2011). A similar isolation frequency from outpatients (57.75%) was reported in Ethiopia (Derese et al., 2016), while a higher percentage recorded in France (83%) (Malmartel & Ghasarossian, 2016) and in Korea (89%) (Park et al., 2017). *E.coli* was the most frequent followed by *Klebsiella*. spp., *Citrobacter* spp, *Proteus* spp and lastly *Enterobacter* spp which were close to what found by Abujnah et al., 2015 and Lyonga et al., 2015. In spite of similarity with these reports, *Citrobacter* isolation (6.7%) remains the highest in the current study.

Regarding antimicrobial susceptibility of Enterobacteriaceae isolates; *Klebsiella* and *Enterobacter* isolates were quite susceptible with lower levels of resistance to all tested antimicrobial agents. *Citrobacter* isolates showed high levels of resistance to most of agents. In general; the highest resistance among Enterobacteriaceae isolates was recorded against SXT with a percentage of 57.5% followed by CRO (49.3%). The wide spread resistance against SXT was also recorded with a percentage of 91.1% in Bo, Sierra Leone (Leski, et al., 2016) and 70.7% in Ethiopia (Kibret & Abera, 2014) while others recorded lower rates of resistance with a percentage of 34.4% in Lybia (Mohammed, et al., 2016) and 31.7% in Korea (Park, et al., 2017). High resistance to Ceftriaxone, probably due to wide spread use in the locality, matched with resistance rates (55%) recorded in Mexico (Ponce-de-Leon et al., 2018) and 50% in Ethiopia (Kibret & Abera, 2014), on the other hand researchers in Lybia recorded resistance rate of 31.9% (Mohammed, et al., 2016).

Of the antimicrobials tested, Enterobacteriaceae isolated from UTI showed a relatively high resistance to each of AMC, CTZ with resistance rates of 36.1%, 32.3% respectively. Park and his colleagues reported lower rates for AMC resistance in Korea with a percentage of 20.7% while they reported very low resistance of 3.9% for Ceftazidime (Park, et al., 2017). Higher resistance rate for AMC was recorded in Libya that reached 47% while moderate resistance of 14.4% was reported against CTZ (Mohammed, et al., 2016).

Moderate resistance was observed to Nitrofurantoin (25%) a commonly prescribed drug in UTI; a number of studies reported high susceptibilities to Nitrofurantoin with a percentage of 94.9%, 97.4% and 98.1% as published by Gunduz & Uludağ Altun, 2018, Aguinaga et al., 2018 and Wong et al., 2017 respectively. On the other hand; high resistance rates against Nitrofurantoin were recorded as 42.1% in Dire Dawa, Eastern Ethiopia (Derese et al., 2016) and 40.9% in Libya (Mohammed, et al., 2016). Nalidixic acid; which is the first of synthetic quinolone antibiotics, had a resistance rate of 32.5% of the isolated Enterobacteriaceae which is close to what recorded in Yaoundé, Cameroon; 35.4% (Lyonga et al., 2015) while 52.6% resistance rate was reported in Dire Dawa, Eastern Ethiopia (Derese et al., 2016) and 49.2% in Iran (Sedighi et al., 2015). Fluoroquinolones had an overall resistance rate of 20.5%, near results were reported in France (17%) (Malmartel & Ghasarossian, 2016) and in Korea (24.8%) (Park et al., 2017). However; high resistance rate was recorded (54.9%) in Asian countries (Choe et al., 2018).

The current study recorded a susceptibility of 80.9% to Amikacin which matched with susceptibility rate recorded previously in the same hospital of 83% (Gad et al., 2011) and 75.1% among hospitalized urology patients in Asian countries (Choe et al., 2018). While others reported susceptibility rates for Amikacin of 100%, 99.1% and 93.9% respectively (Mohammed, et al., 2016, Park, et al., 2017 and Zhao et al., 2015). None of isolates were resistant to Imipenem. High susceptibility of Enterobacteriaceae isolated from UTI to IMP was recorded as 99.4% in Libya (Mohammed, et al., 2016), 99.7% in

Korea (Park, et al., 2017) and 100% in China (Zhao et al., 2015).

In conclusion, we found that different risk factors lead to increased number of patients that are prone to UTIs. Different bacterial species were responsible for UTI with E-coli being the most frequently isolated pathogen and interestingly a higher percentage of *Citrobacter* species than previously published studies. Emergence of MDR Enterobacteriaceae strains can make the treatment difficult, so we recommend antimicrobial susceptibility testing. According to our results Imipenem, Amikacin, Fluoroquinolones and Nitrofurantoin are the most effective agents against Entero-bacteriaceae species isolated from UTI.

Conflict of Interests: The authors declare no conflict of interests regarding the publication of this paper.

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