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RESEARCH ARTICLE

ANTIBIOTIC SUSCEPTIBILITY PATTERNS OF COMMUNITY AND HOSPITAL ACQUIRED URINARY ISOLATES OF ESCHERICHIA COLI

[1, 2]Fouzia Haider, [3]Bashayer Matar Quhimea Al-huthali, [3]Reem Ahmed Khalaf Alghuraybi, [3]Ghadeer Jassim Mohammad Zahiri and [3]Wejdan Mustafa bakur Barnawi

[1]Department of Microbiology, University of Karachi, Pakistan
[2]Former Assistant Professor, Department of Laboratory Medicine, Faculty of Applied Medical Sciences, Umm Al Qura university, Makkah, Saudi Arabia
[3]Department of Laboratory Medicine, Faculty of Applied Medical Sciences, Umm Al Qura University, Makkah, Saudi Arabia

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ABSTRACT

Background: *Escherichia coli* accounts for majority of community and hospital acquired urinary tract infections in many parts of the world. It has developed resistance against antimicrobial agents and it is necessary to have up to date knowledge of drug resistance pattern for treatment of UTIs caused by this organism. **Objective:** To determine and compare antimicrobial susceptibility patterns of urinary. *E.coli* isolated from patients with community and hospital acquired UTIs in Makkah Saudi Arabia. **Materials and Methods:** This prospective descriptive study was performed for a period of three months. A total of 92 *Escherichia coli* isolated from urine samples were collected from four hospitals of Makkah. The clinical and demographic information of the patients was collected using a predesigned questionnaire. Isolates were confirmed by using bacteriological methods and API 20E kits. All *E.coli* strains were subjected to in vitro susceptibility testing using Kirby Bauer disk diffusion method as described in CLSI guidelines. **Results:** The study was performed in patients of all age groups and both the genders. Majority of the patients were in age group1-10 years and 21-30 years in community acquired infections and1-10 years followed by 21-30 years and 70-80 years in hospital acquired infections. A predominance of female patients (73%) compared to male patients (27%) was seen. Majority of the urinary tract infections were community acquired (55%) compared to hospital acquired (45).Over all antibiotic resistance data of 92 isolates showed low to high resistance to all drugs tested (2.17-100%). The highest resistance was exhibited by ampicillin (100%) followed by cephalothin (65.2%) and trimethoprim/sulphamethoxazole (64.1%). The rates of drug resistance for other antibiotics were: cefuroxime 36.9%, norfloxan29.3%, levofloxacin 28.2%, ceftazidime 18.4 %, amoxicillin/clavulanic acid 14.1%and cefoxitin 11.9%. Among all antibiotics tested imipenem showed lowest resistance (2.17%). In summary, highest resistance was seen against ampicillin followed by cephalothin and trimethoprim/sulphamethoxazole and least resistance was shown against imepenim. Moreover, higher resistance was seen in hospital acquired infections compared tocommunity acquired infections. Very high level of MDR was also seen (60%) among isolates from all the hospitals. **Conclusion:** This study showed low to high drug resistance of *E.coli* isolates from various hospitals of Makkah. Alarming rates of MDR among community acquired as well as nosocomial isolates call for continuous periodic monitoring in Makkah region to know the developing resistance pattern which, will help in deciding the most adequate therapy for *E.coli* urinary tract infections.

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INTRODUCTION

E.coli is the commonest cause of community and hospital acquired urinary tract infection in many parts of the world and antibiotic resistance pattern showed variation in both settings (1-3). Antibiotic resistance among community acquired urinary tract infections is reported from all over the world including Korea (4) Nigeria (5) northern Italy (6), UK (7) and USA (8) etc. The situation is compounded by the fact that multidrug resistant *E.coli* infections have also been reported from around the globe. Studies from Latin America (9), Africa (10), Australia (11), India (12), Pakistan (13), UAE (14) and Saudi Arabia (15) show increased resistance to first-line agents likes ampicillin, nitrofurantoin, and trimethoprim–sulphamethoxazole as well as gentamicin, ciprofloxacin and/or

third-generation cephalosporins, flouroquinolones and extended-spectrum beta-lactams. Antibiotic resistance among hospital acquired urinary tract isolates is found to be much higher than community acquired isolates (16). The prevalence of resistance in *E.coli* both to single antibiotic and multi-drugs continues to increase in Europe. The resistance of *E.coli* against third generation cephalosporin for ESBL-production, imipenem and/or meropenem reported from Hungary and Australia (17-18). Studies from USA (1) Africa (19), Ethiopia (20), Iran (21), India (22). Pakistan (23) and Saudi Arabia (24-25) also report a high rise in antibiotic resistance pattern of hospital acquired *E.coli* urinary tract infections. The antimicrobial resistance patterns of uropathogenic *E.coli* from around the world are at rise which is a matter of grave concern. Since treatment of UTI is frequently started empirically, which usually follows the known susceptibilities of urinary pathogen in that community, whereas multidrug resistance limits these therapeutic choices. It, therefore, is utmost important to have current knowledge on antimicrobial susceptibility pattern in a particular region which is essential for appropriate therapy of *E.coli* UTIs. Therefore, the objectives of the study were to determine antibiotic susceptibility patterns of *E.coli* isolated from patients with community and hospital acquired UTIs in Makkah region, to determine the magnitude of multidrug resistance among clinical *E.coli* isolates to suggest appropriate antibiotics for empirical therapy.

MATERIALS AND METHODS

The study was carried out at the Department of Laboratory Medicine, Faculty of Applied Medical Sciences, Umm Al Qura University, Makkah, Saudi Arabia after approval by the ethical committee. The participating hospitals included Al-Noor hospital, King Abdul-aziz hospital, Maternity and Children hospital and Security forces hospital. The clinical data of the patients was collected using a predesigned questionnaire and all information was obtained with the help of hospital staff from patient's file. The identification of *E. coli* was done by using API 20E Kits (BioMerieux). The isolates were tested for antimicrobial susceptibility on Muller Hinton agar (Biolab) according to the guidelines of Clinical and Laboratory Standards Institute (CLSI, 2012). As per CLSI recommendation antibiotic disks (Oxoid) were used for antimicrobial susceptibility. The antibiotics included amikacin (30µg), ampicillin (25µg), cefepime (30µg), ceftazidime (30µg), cefoxitin (30µg), cefuroxime (30µg), imipenem (10µg), levofloxacin (5µg), piperacillin (100µg), piperacillin–tazobactam (100/10µg), trimethoprim-sulphamethoxazole (1.25/23.75µg), norfloxacin (5µg), cephalothin (30µg), and amoxicillin/clavulanic acid (20/10µg).

RESULTS

A total of 92 *E.coli* strains isolated from urine specimens of patients, from both community acquired and hospital acquired UTI, in various hospitals of Makkah region were studied. These isolates were recovered from both genders of all ages. The patients were in various age groups ranging from less than 1 year to more than 80 years. Majority of them were in age group 1-10 years (25.4% and 26.8% in CAI and HAI respectively), followed by 21-30 years (25.4% and 14.6% in CAI and HAI respectively) and in age group 71-80 (14.6% in HAI) (Table 1). Gender wise data of *E.coli* urinary tract infection showed a high prevalence in females (73%) as compared to males (27%) and female to male ratio was 2.7:1.0 (Figure 1). Out of 92 urine samples from patients clinically diagnosed as Urinary Tract Infections studied, 55% were community acquired infections and 45% hospital acquired infections (Figure 2). Distribution of *E. coli* isolates among the hospitals of Makkah according to the type of infection is shown in the Table 2. The most hospital acquired urinary infections were from Al-Noor hospital (100%) followed by King Abdul-aziz hospital and Maternity and Children hospital (44.44% each). While community acquired urinary infections were reported in highest number in Security forces hospital (67.7%). Collectively, the prevalence of hospital acquired urinary tract Infections from four hospitals was approximately 49% in Maternity and Children Hospital, 24% in Security forces Hospital, 10% in King Abdul-Aziz Hospital and 17% in Al-Noor Specialist Hospital (Supplementary data Figure S1). Community acquired *E. coli* UTIs were reported mostly from Maternity and Children Hospital (49%) followed by 41% from Security forces Hospital, 10% from King Abdul-Aziz Hospital (Supplementary data Figure S2).

Antibiotic Resistance in *E. coli* Isolates: The *in vitro* susceptibilities of the isolates from community acquired and hospital acquired UTIs are determined against 13 antibiotics of various groups. The overall drug resistance data of 92 *E. coli* strains showed low to high resistance to all drugs tested (2.17% to 100%). The highest resistance was exhibited to ampicillin (100%) followed by cephalothin (65.2%) and trimethoprim/sulphamethoxazole (64.1%). The rates of drug resistance to other antibiotics were: cefuroxime 36.9%, norfloxan 29.3%, levofloxacin 28.2%, ceftazidime 18.4 %, amoxicillin/clavulanic acid 14.1% and cefoxitin 11.9%. Less than 10% resistance was shown to all including cefepime (8.69%), amikacin (4.3%) and piperacillin/tazobactam (4.3%). Among all antibiotics tested imipenem showed lowest resistance (2.17%) (Figure 3).

The drug resistance pattern of clinical isolates of *E. coli* recovered from CA and HA urinary tract infections from all the hospitals (Table 3) showed very high resistance to ampicillin followed by trimethoprim/ sulphamethoxazole and cephalothin. High to moderate resistance was also seen for levofloxacin, norfloxacin and cefuroxime. Hospital wise distribution and drug resistance pattern of *E. coli* clinical isolates among the four hospitals of Makkah (Table 4) showed that Maternity and children Hospital isolates have highest drug resistance to ampicillin (100%) followed by trimethoprim/sulfamethoxazole (68.9%), cephalothin (51.1%),cefuroxime (33.33%), norfloxacin (13.33%), levofloxacin (11.1%), ceftazidime (8.88%), cefepime and amoxicillin/clauvlanic acid (6.66% each) and cefoxitin (4.44%). *E. coli* isolates from this hospital did not show any resistance to amikacin, imipenem and pipericillin/ tazobactam. The clinical *E. coli* isolates from Al-Noor Specialist Hospital showed high drug resistance (14.3%-100%) to the antibiotics tested. The highest resistance was shown against ampicillin, norfloxacin and levofloxacin (100% each) followed by cephalothin (85.7%), cefuroxime (71.4%), trimethoprim/ sulfamethoxazole (57.1%) and ceftazidime (42.8%). cefoxitin and pipericillin/tazobactam showed equal rate of resistance (28.6%, each). The isolates from this hospital did not show any resistance to amikacin. The clinical *E. coli* isolates from Security Forces Hospital, showed highest drug resistance to ampicillin (100%). This is followed by cephalothin (80.6%), trimethoprim/sulfamethoxazole (61.3%). *E. coli* showed lowest resistance to imipenem (3.22%).

Table 1. Distribution of *E.coli* UTI according to Age, Sex and type of infection

Age Group (years)	CAI			HAI		
	Male	Female	Total (%)	Male	Female	Total (%)
< 1	1	-	1 (1.96%)	-	1	1(2.4%)
1 – 10	3	10	13(25.4%)	2	9	11 (26.8%)
11- 20	1	1	2 (3.9%)	0	1	1 (2.4%)
21 – 30	2	11	13 (25.4%)	1	5	6 (14.6%)
31 – 40	1	5	6 (11.7%)	-	4	4 (9.7%)
41 – 50	-	4	4 (7.8%)	-	1	1(2.4%)
51 – 60	2	1	3 (5.8%)	3	1	4 (9.7%)
61 – 70	-	4	4 (7.8%)	-	3	3 (7.3%)
71 – 80	1	2	3 (5.8%)	4	2	6 (14.6%)
> 80	1	1	2 (3.9%)	3	1	4 (9.7%)
Total	12(23.5%)	39(76.4%)	51 (100%)	13 (31.7%)	28 (68.9%)	41(100 %)
Total Males in all age Groups	12	-		13		25 (27.2%)
Total Females in all age Groups	-	39	-	-	28	67 (72.8%)

Table 2. Distribution of *E. coli* isolates according to the type of infection in various hospitals

Name of Hospital	Infection type of *E. coli* isolates according to hospital No(%)	
	Community acquired infection (n=51)	Hospital acquired infection (n=41)
MCH (45)	25 (55.5%)	20 (44.4%)
NH (7)	-	7 (100%)
SFH (31)	21 (67.7%)	10 (32.2%)
KAH (9)	5 (55.5%)	4 (44.4%)

MCH =Maternity and Children Hospital; NH = Al-Noor Specialist Hospital; SFH= Security forces Hospital; KAH= King Abdul-Aziz Hospital.

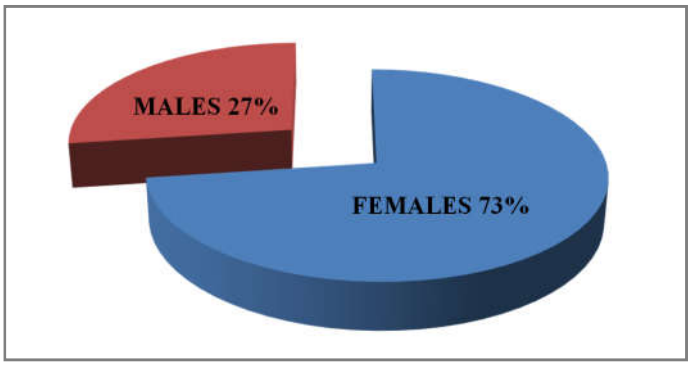

Figure 1. Distribution of *E.coli* urinary tract infections according to gender.

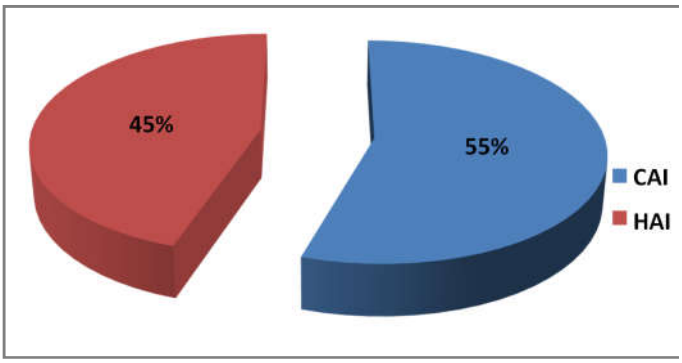

Figure 2. Distribution of *E.coli* urinary tract infections according to type of infection

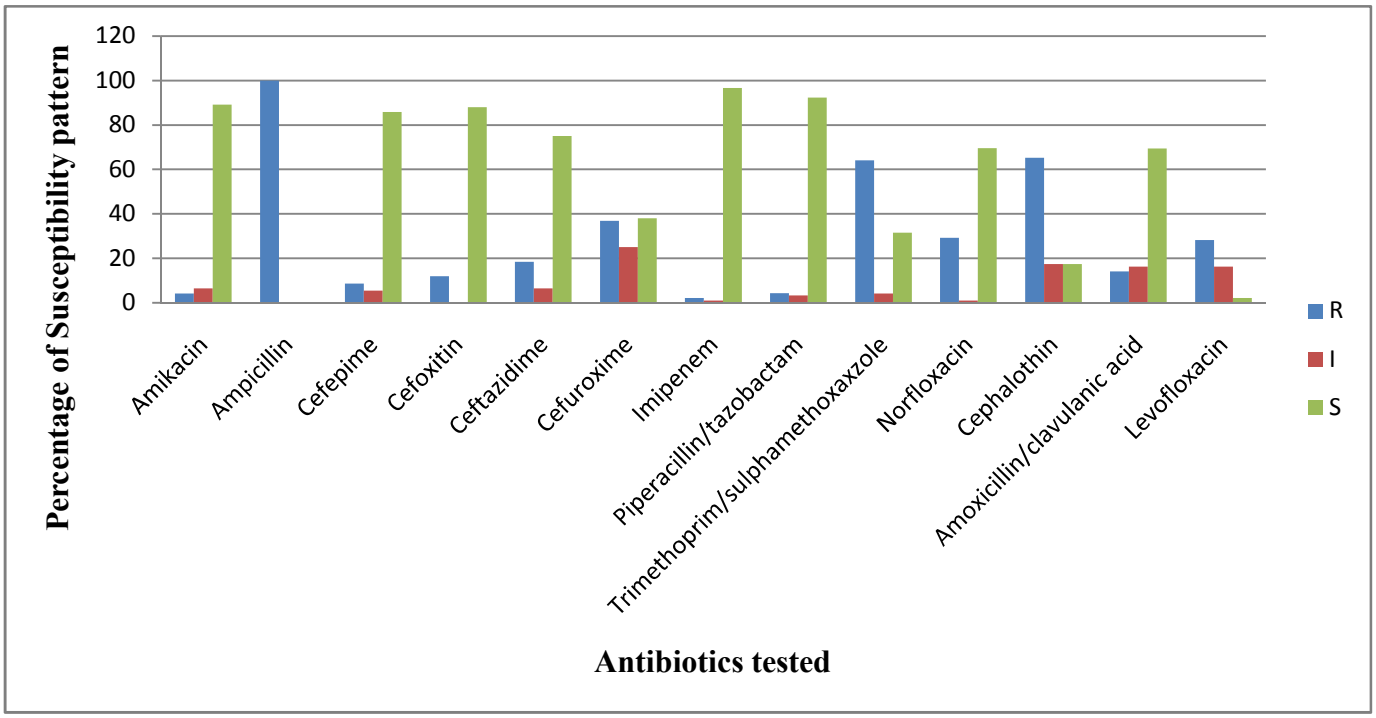

Figure 3. Overall percentages of drug resistance in *E. coli*.

Table 3. Resistance pattern of *E. coli* isolates according to the type of infection

Name of antibiotics	Resistance pattern of isolates by infection type No (%)	
	Community acquired infection (n=51)	Hospital acquired infection (n=41)
Amikacin	3(5.8%)	1 (2.43%)
Ampicillin	51 (100%)	41 (100%)
Cefepime	4 (7.8%)	4 (9.7%)
Cefoxitin	6 (11.7%)	5 (12.1%)
Ceftazidime	9 (17.6%)	8 (19.5%)
Cefuroxime	17 (33.3%)	17 (41.4%)
Imipenem	1 (1.9%)	1 (2.4%)
Piperacillin/tazobactam	2 (3.9%)	2 (4.8%)
Trimethoprim/sulphamethoxazole	31 (60.7%)	28 (68.2%)
Norfloxacin	13 (25.4%)	14 (34.1%)
Cephalothin	33 (64.7%)	27 (65.8%)
Amoxicillin/clavulanic acid	6 (11.7%)	7 (17%)
Levofloxacin	12 (23.5%)	14 (34.1%)

Table 4. Antibiotic resistance pattern in hospitals of Makkah

Name of Hospital	Antibiotic resistance pattern in participating hospitals												
	AK	AM	FEP	FOX	CAZ	CXM	IPM	TPZ	CXT	NOR	KF	AMC	LEV
MCH (45)	0	100	6.66	4.44	8.88	33.3	0	0	68.9	13.3	51.1	6.66	11.1
NH(7)	0	100	14.3	28.6	42.8	71.4	14.3	28.6	57.1	100	85.7	14.3	100
SFH (31)	12.9	100	12.9	16.1	29	35.4	3.22	6.4	61.3	38	80.6	22.6	38.7
KAH (9)	0	100	0	22.2	11.1	33.3	0	0	55.6	22.2	66.7	22.2	22.2

MCH= Maternity and children hospital; NH= Al-Noor Specialist Hospital; SFH= Security forces Hospital; KAH= King Abdul Aziz Hospital

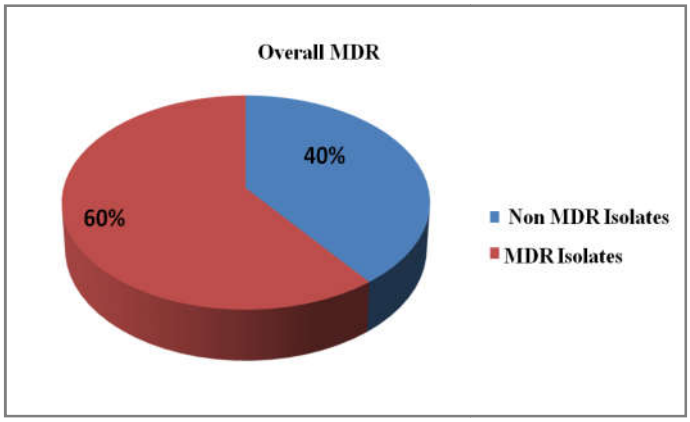

Figure 4. Overall multidrug resistance (MDR) among *E.coli* isolates

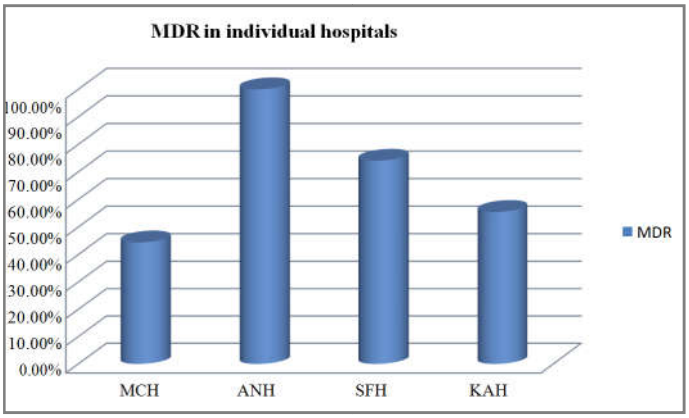

Figure 5. Multidrug resistance among *E. coli* isolates in individual hospitals

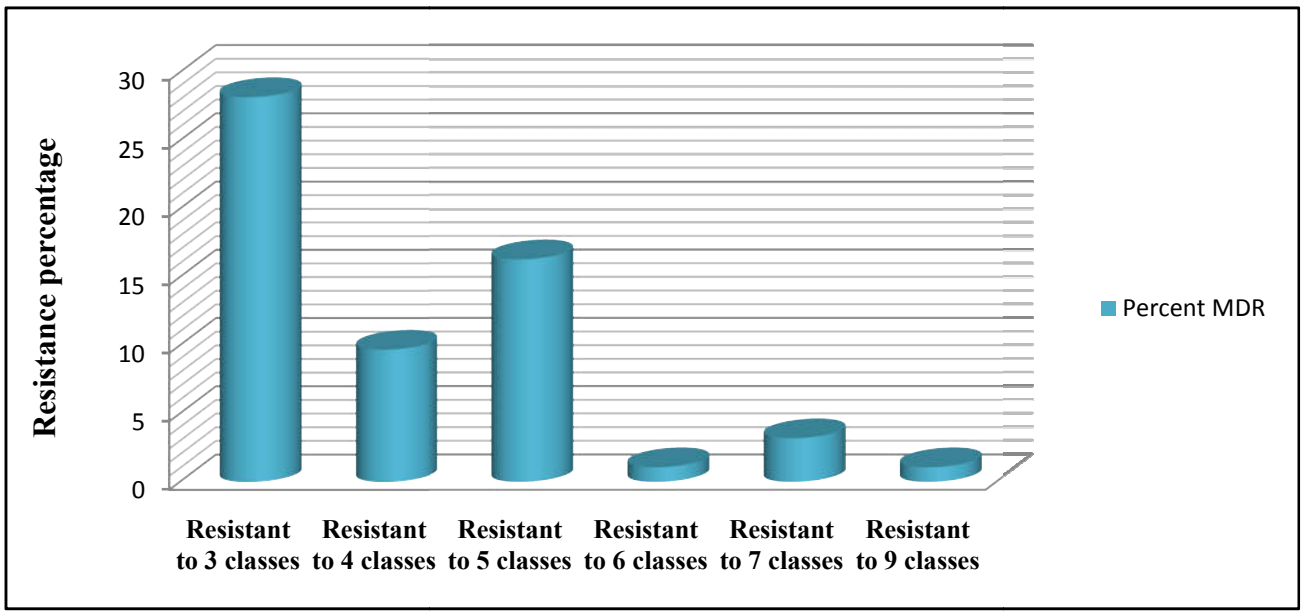

Figure 6. Distribution of MDR among *E. coli* isolates to various classes of antibiotics. The antibiotic classes included;1. Aminoglycosides; 2.β-lactamase inhibitors; 3. Carbapenems; 4. Non extended spectrum cephalosporins; 5. Extended spectrum cephalosporins; 6. Cephamycins; 7. Fluoroquinolones; 8. Folate pathway inhibitors; 9.Penecillins;10; Penecillin with β-lactamase inhibitor

The drug resistance rate exhibited by *E. coli* isolates from King Abdul Aziz Hospital varied from 11.11% -100%, with the highest drug resistance to ampicillin and lowest to ceftazidim. Moderate resistance rate was shown to cefoxitin, norfloxacin, ampicillin/clavulanic acid and levofloxacin (22.22% each). The strains did not show any resistance to amikacin, cefepime, imipenim and pipericillin/tazobactam. Overall Multidrug resistance (MDR) was found to be 60% among the isolates studied (Figure 4). The *E.coli* isolates from Al-Noor Specialist Hospital were resistant to most of the antibiotics tested (100%). Next in order were Security Forces Hospital (74.1%), King Abdul Aziz Hospital (55.5%) and Maternity and Children Hospital (44.4%) (Figure 5). Among MDR isolates the resistance pattern varied and resistance to antibiotics of various classes was: 28.8% resistant to three antibiotics, 9.7% resistant to four antibiotics, 16.3% resistant to five antibiotics, 1.08% resistant to six antibiotics, 3.2% resistant to seven and 1.08% resistant to nine antibiotics (Figure 6).

DISCUSSION

Among bacteria *Escherichia coli* is the primary cause of most urinary tract infections, accounting for majority of community and hospital acquired urinary tract infection in many parts of the world (1-3). In this study a predominance of very young and young females was seen in community as well as hospital acquired infections. Our data is in agreement with the studies from Bangladesh which report predominance of young females in community and hospital acquired urinary tract infections (26). The predominant group of very young males was also seen in Community acquired infections whereas in older age group 51-60 years, males were more affected than females. These findings coincide with the findings from Bangladesh, which indicate that older male age groups of 60 years and above were more affected than females (26). This trend can be attributed by increased incidence of urinary tract pathologies like prostate diseases in older age. The gender has specific preference for urinary tract infections. The prevalence of urinary tract infections is high in females as compared to males in both community and hospital acquired infections as suggested by local studies done in Saudi Arabia (24,27,28) as well as reported from other parts of the world (29-30). This study reports 73% females and 27% males had UTI similar to the findings in Bangladesh 71.1% females and 28.9% males (26) and 76% females and 24% males in Saudi Arabia (24). The factors contributing towards less susceptibility of males to acquire UTI, as compared to females, are possibly longer course of urethra and bacteriostatic properties of prostate secretions. The prevalence of community and hospital acquired UTI varies throughout the globe. In UK more community acquired infections were reported (88.7%) compared to HAI (11.8%) (7). Similarly, studies from India and Saudi Arabia (Jeddah) showed higher rates of CAI (60%) as compared to HAI (40%) (31) and CAI (31.6%) compared to HAI (29.6%) (32), respectively. These findings are similar to our findings where CAIs are higher (55%) compared to HAIs (45%). However, studies from various other parts of Saudi Arabia show higher prevalence of HAIs for example previous studies from Makkah and Qassim showed 65.3% HAI compared to 34.7% CAI (25) and 48.1% HAI compared to 43.2 % CAI (33). This trend may account for, relatively, suboptimal infection control measures in different hospitals of Saudi Arabia in past. Antibiotic resistance is one of the major problems in treating urinary tract infections caused by *E. coli*. The treatment relies on the susceptibility data from local surveillance studies; therefore, in this study antibiotic resistance levels of *E.coli* to various antibiotics were determined, which showed low to very high resistance pattern against all the antibiotics tested (2.17% to 100%).Other countries including USA (8, 34), Canada (1), India (22, 31), Saudi Arabia (15, 24, 25, 32,) also reported higher antibiotic resistant levels of *E.coli* isolates causing UTI. This study shows highest resistance against ampicillin (100%) in community acquired and nosocomial infections. Very similar finding, 100% ampicillin resistance, was also reported from Pakistan (13**),** Saudi Arabia (24) and highest resistance rate against ampicillin reported from Iran (35), India (22), Benin (36) and USA (8). These findings suggest a very high resistance against ampicillin around the globe. In this study the resistance to Cephalothin was 65.2%. Studies from USA also showed high resistance to this drug (86.6%) (34). However, variable resistance (45.5%) has also been reported (9). This variation in resistance could be a reflection of inappropriate use of relevant antibiotics in various settings**.** Resistance of *E.coli* to trimethoprim/sulphamethoxazole is variably reported around the globe, from Latin America (38.6%)(9);Benin (86.9%)(36**);** USA (92.8%) (34).Our study showed 64.1% resistant to this antibiotic which is in agreement with the studies from India (67% from community isolates) (37). However, from within Saudi Arabia an on rise trend of the antibiotic resistance with the passage of time can be clearly seen**;** Daharan (33% CAI and 44% HAI) (15); Jeddah (44 and 52%, CAI and HAI respectively) (32);Al-Quwayiyah (54.7%, HAI) (38) and our studies 64.1%.

In this study, a moderate to low resistance was observed against cefuroxime (36.9%) and ceftazidime (18.4 %) respectively. Which are similar to studies from India which showed 44% cefuroxime and 16% ceftazidime resistance (31); from Saudi Arabia cefuroxime (21.4%) and ceftazidime (9.8%) (32) from community isolates. Another study from Saudi Arabia reported lower rate of resistance for ceftazidime (9 % CAI- 17% HAI) (15**).** The resistance to other cephalosporins, shown in this study, were cefoxitin (11.9%) and cefepime (8.69%). cefoxitin resistance reported from Latin America (13.4%) (2) and Saudi Arabia (13.2%) in hospital isolates (38) are in agreement with our results. Cefepime resistance reported from India was 16%-20% (31) and Saudi Arabia 8.6%-22.4 % (32) for both community and nosocomial infections respectively**.** However, very low rates were reported from Latin America **(**3.1%) from nosocomial isolates (2). A rise in resistance to 4th generation cephalosporin, Cefepime, reflects inappropriate use of relevant antibiotic for the treatment of urinary infections. The resistance to norfloxacin, in this study, was 29.3% followed by levofloxacin 28.2%. This is comparable with the rates reported in Jeddah, Saudi Arabia, norfloxacin (19.7 and 40%) and levofloxacin (36.4-33.3%) in community and hospital acquired infections respectively (32).A study from Qassim, Saudi Arabia, showed 49% Norfloxin resistance (33**),** from Benin 53.6% norfloxacin resistance from nosocomial isolates was reported(36),(5% and 0%) from India (31). The variation is related to the intensity of use of flouroquinolones in various parts of the world. Resistance of *E.coli* to amoxicillin/clavulanic acid is becoming a rising problem in developing countries. Studies from Pakistan (13**)** and India (37**)** showed very high resistance 100% and 80% respectively among community isolates. Higher rates are also reported from Benin 85.7% resistance in nosocomial isolates (36); 70.1% resistance from community and 37.7% resistance from hospital isolates were reported from Jeddah

Saudi Arabia (32) and 37% from UAE (14).However, variable and lesser resistant rates were reported from other countries; 12% from UK (7**)** and 18.61% from Latin America (9**)** which are comparable with the rates reported in our study (14.1%). In this study, the nosocomial isolates exhibited a high degree of drug resistance as compared to community isolates except only for Amikacin where community acquired isolates were slightly more resistant. This study showed an overall high drug resistance among the isolates of four participating hospitals of Makkah, although, each hospital had a variable rate of antibiotic resistance. The isolates of Maternity and Children hospital showed sensitivity to Amikacin, Imipenem and piperacillin/tazobactum. Amikacin was the only drug, which showed sensitivity to all the isolates from Al-Noor Specialist hospital. Isolates of Security forces were the most resistant and showed least resistance to imepenim. However, all the isolates from King Abdul-Aziz hospital were sensitive to imepenim.

Collectively, among all antibiotics tested Imipenem, Amikacin and piperacillin/tazobactum showed lowest resistance and can be used as drug of choice for therapeutic purposes after obtaining antibiogram of individual cases/isolates. This study demonstrated very high resistance of individual isolates and various trends of resistance to various classes of antibiotics. It was quite alarming to note that majority of the isolates were resistant to more than three classes of antibiotics thus fulfilling the criteria of being classified as MDR. The total percentage of isolates classified as MDR was 60% of all the isolates tested in this study. Which is very high then other reports of multidrug resistance from Saudi Arabia, Daharan, which detected MDR in 2.0%-28.1% of outpatient isolates and 7.4%-39.6% of inpatient isolates, depending on the combination of antimicrobials tested (15). Studies from Pakistan declared 81% of total *E.coli* isolates causing UTI were MDR (23). These findings call for continuous periodic monitoring in Saudi Arabia, especially Makkah, to be aware of alarming level of resistance of bacteria involved in causing UTI. Thus, helping the physicians to prescribe the drugs cautiously.

Conclusion

This study has identified very high resistance of *E.coli* against most commonly used antibiotics to treat urinary tract infections from four hospitals of Makkah. In all the hospitals the most resistant antibiotics was ampicillin. Furthermore, this study also concludes that *E. coli* was more sensitive to imipenem, amikacin and piperacillin/tazobactum compared to other antibiotics tested and arepromising to be used as drug of choice to treat urinary tract infections. A very high multidrug resistance was found in *E.coli* showing resistance to as high as up to nine classes of antibiotics tested.

Abbreviations

AK - Amikacin
AM - Ampicillin
AMC - Amoxicillin/clauvlanic acid
API 20E - Analytical profile index 20 Enterobacteriaceae
CAZ - Ceftazidime
CLSI - Clinical and laboratory standards institute
CXM - Cefuroxime
CXT - Trimethoprim/sulfamethoxazole
E. coli - Escherichia coli
ESBL - Extended spectrum β-lactamase
FEP - Cefepime
FOX - Cefoxitin
IPM - Imipenem
KF - Cephalothin
LEV - Levofloxacin
MDR - Multidrug resistance
mm - Millimeter
NOR - Norfloxacin
TPZ - Piperacillin-tazobactam
UK - United Kingdom
USA - United States of America
UTIs - Urinary tract infections

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SUPPLEMENTARY DATA

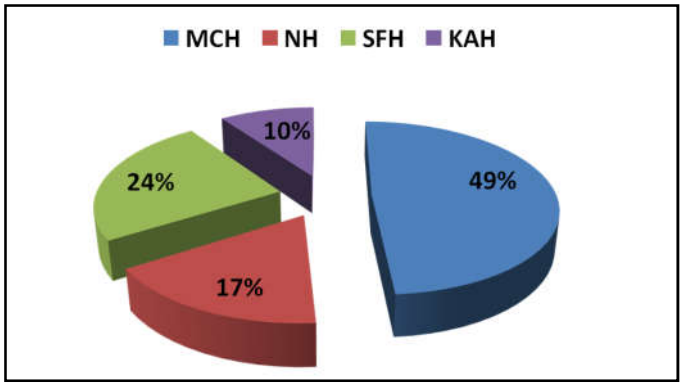

Figure S1. Distribution of HA infections in various hospitals of Makkah

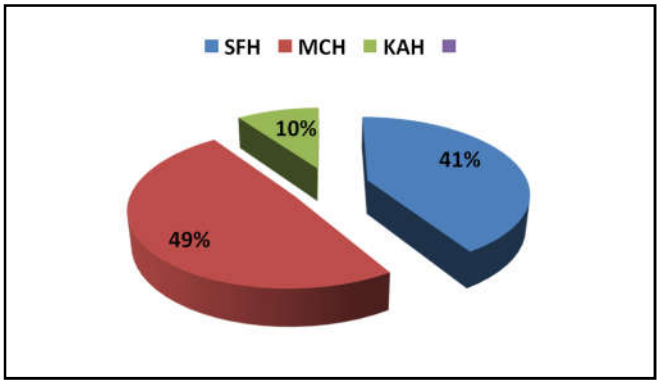

Figure S2. Distribution of CA infections in various hospitals of Makkah

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